ETS: LUNG CANCER

VOLUME II

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC, COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE HIGHLIGHT).

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ADDITIONAL STUDIES DISCUSSING LUNG CANCER

In addition to the primary lung cancer studies discussed in Section A of this notebook, a number of other studies are sometimes cited in support of claims that ETS exposure is associated with an increased risk of lung cancer. The studies fall into two categories: some are case-control studies similar to the primary studies, and some are studies of other aspects of lung cancer.

Following are brief summaries of these studies, including discussions of their problems and limitations. Copies of these studies follow this introduction, arranged in chronological order and highlighted in yellow for useful information and in blue for adverse information.

Case-Control Studies

While the studies in this category present risk estimates similar to those calculated in the primary epidemiologic studies on spousal smoking, incomplete information or methodological differences preclude their inclusion in that set of studies. Difficulties with the earliest studies in this group (e.g., Knoth, et al., 1983; Miller, 1984; Sandler, et al., 1985) were apparently recognized by the National Academy of Sciences (1986) and the Environmental Protection Agency (1990), neither of which included these studies in their meta-analyses. In his 1992 book on ETS,

Peter Lee justifies his decision not to include a number of these studies as well.

Knoth, et al., 1983

- This German study included a total of 792 lung cancer patients. However, there was no control population for comparison, and thus, the authors' conclusions are of limited value.[1]

- One reviewer commented that this report contained "only tentative conclusions based on poor data analyzed by unacceptable methods."[2]

Sandler, et al., 1985

- Although the papers published by Sandler, et al., in 1985 focused on overall mortality, some numbers of lung cancer deaths were presented.[3]

- The methodology and interpretation of these studies have been heavily criticized (e.g., one scientist described the studies as "heavily flawed").[4] The data presented are of limited value.

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- As noted by Peter Lee, the Sandler data are based on only two reported lung cancer deaths.

Dalager, et al., 1986

- Data from three case-control studies conducted in the United States under the auspices of the National Cancer Institute were combined and analyzed in this study.[5] (Two of the studies, Correa, et al., and Buffler, et al., were discussed in Section A of this notebook.)

- Because the Dalager paper includes two primary studies on ETS and lung cancer, if it were included in considerations of the epidemiologic studies, it would result in some data being "counted" twice.

Lloyd, et al., 1986

- In a study investigating the high rate of lung cancer in one town in Scotland, relatives of 42 cases who had died of lung cancer and of 42 matched controls who had died of other causes were interviewed.[6]

- Conclusions about ETS exposure were based on smokers and nonsmokers combined, thus precluding comparisons to the primary

studies cited in Section A of this notebook. However, the authors reported no statistically significant differences between cases and controls for any questions relative to personal smoking or to ETS.

Katada, et al., 1988

- This study, using hospitalized individuals in Nara, Japan, included only 25 female lung cancer cases (some of whom were smokers) and 50 female controls.[7]

- All of the cases reported present exposure to ETS, all but two reported past exposure, and all but four reported childhood exposure. Thus, the reference categories (i.e., non-exposed women) are too small to allow appropriate calculations of relative risk.

- Nevertheless, none of the case-control comparisons was statistically significant at the 5% level. (Note: the paper also bases some of its conclusions on nonsmokers and smokers combined.)

- The Katada, et al., study was mentioned in the 1992 EPA Risk Assessment on ETS, but its data were not used in any analyses.

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Lam and Cheng, 1988

- This paper reviews four lung cancer studies previously conducted in Hong Kong, all of which are presented in the Primary Studies section of this notebook.[8] [Note: Because only a few pages of the 1985 W.K. Lam thesis are available, the Lam and Cheng article provides the best source for W.K. Lam's data and risk estimate.]

- Using meta-analysis, Lam and Cheng calculate a statistically significant summary point estimate for the four studies.

Chen, et al., 1990

- In 1990, conclusions based on a study of 332 cases and 635 group-matched hospital controls in Taiwan were published.[9]

- For ETS exposure, point estimates achieving statistical significance were reported; however, it appears that these risk estimates were calculated using both nonsmokers and active smokers, and are thus not comparable with those reported in other studies based on nonsmokers only.

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Miller, 1990

- Miller used newspaper death notices to ascertain cancer deaths in women in northwestern Pennsylvania, and then interviewed surviving next-of-kin to obtain information on the deceased women. This approach could be expected to result in problems related to accurate recall by those interviewed.[10]

- In a 1984 paper, Miller examined "all cancer deaths" (See Other Cancers section in this notebook); in the 1990 paper, he provides numbers of cancer deaths by site.

Holowaty, et al., 1991

- This paper reports on a study of 51 female lung cancer cases and 45 controls.[11] Only five cases and 27 controls were reported to be never smokers.

- Presumably due to the small sample size, Holowaty, et al., do not present risk estimates based on nonsmokers alone; their risk estimates for household ETS exposure are all adjusted for personal smoking history. None of the reported risk estimates is statistically significant.

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Liu, et al., 1993

- This recent paper discusses indoor air pollution and lung cancer incidence in a Chinese population, and briefly presents data on reported ETS exposures.[12]

- The paper does not provide key information necessary for evaluation of its conclusions. For instance, the derivation of the exposure index used ("cigarette equivalents") is not provided, nor do the authors define "nonsmoker."

- No overall risk estimate is given in the paper. Rather, the authors provide separate risk estimates for two levels of husband's smoking. One of these is less than 1.0; the other is statistically significantly elevated.

Wang, et al., 1993

- At first glance, this meeting abstract appears to present usable data on childhood ETS exposure and lung cancer.[13] It reports several statistically significant risk estimates.

- However, the authors do not indicate if their analyses were restricted to nonsmokers. Given that cases and controls were reportedly matched on "lifetime smoking habits," it appears

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probable that the reported risk estimates were derived from both smokers and nonsmokers, thus making them incompatible with the risk estimates in the primary studies.

Other Epidemiologic Studies

In addition to the above-described studies, the following studies have also been cited in support of claims of lung cancer risk associated with ETS exposure.

Trichopoulos, et al., 1992

- In this study, conducted in Athens, Greece, lung tissue samples taken at autopsy were examined for cellular changes.[14] The authors claimed that levels of "epithelial, possibly precancerous lesions" were statistically significantly elevated in specimens of lung tissue from women whose husbands reportedly smoked.

- The cellular changes examined in this study were considered "lung cancer risk indicators" by the authors. However, the persons included in the study died of causes other than cancer or respiratory disease.

- Although the study included 400 persons, the data on nonsmoking women came from a small group of only 41 women. Of that group, 17 were reportedly married to husbands who smoked and 13 were married to nonsmokers. The remaining eleven were not included in the analysis because "relevant information was not available."

- The authors report a higher incidence of cellular changes among individuals reportedly exposed to ETS (an odds ratio of 6.0) than for active smokers (an odds ratio of 4.4).

- Air pollution is a potential contributor to the types of cellular changes reported in the study. Indeed, Athens is reportedly one of the most heavily polluted cities in the world.

Reif, et al., 1992

- In an abstract and brief paper, these authors report on a case-control study of lung cancer in pet dogs reportedly exposed to their owners' cigarette smoke.[15]

- The study reports a statistically nonsignificant risk estimate for exposure to a smoker in the home. It also suggests that the reported risk was highest in dogs with short- or medium-

length noses, compared to long-nosed breeds. The authors propose that epidemiologic studies of pets "may add to our understanding" of ETS.

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PASSIVE SMOKING AS A CAUSATIVE FACTOR OF LUNG CANCER IN NONSMOKING WOMEN

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PASSIVE SMOKING AS A CAUSATIVE FACTOR OF LUNG CANCER IN NONSMOKING WOMEN

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ABSTRACT:

In a study on 792 patients with bronchogenic carcinoma of both sexes in the region Mannheim–Ludwigshafen–Heidelberg 59 female bronchogenic carcinomas were found. 39 of them appeared in non-smoking female patients. 61.5% of them had lived in domestic community with smokers. This is nearly the threefold as could be expected on the basis of smoking behavior of men in the respective groups of age. Suggestions on professional exposition to cancerogenic substances could not be found just as little as references to hereditary factors. Passive smoking is by far the obvious interpretation for the high share of non-smokers in our female patients with bronchogenic carcinoma the more so since the percentage of squamous cell and small-cell carcinomas which are valid as typical carcinomas of smokers, did not lie essentially lower in our non-smoking wives (66.6%) in comparison to female smokers (80%). As a further support of this interpretation is refered to similar results in the world literature proving our findings as not surprising.

In a study on 792 lung cancer patients published in a previous paper (Med. Klin. Prax., 1/1983) we had investigated the question of whether "light smoking" (smoking of filter-tipped cigarettes) reduces the lung cancer risk, and had found at least five indicators to refute this hypothesis. However, we also came upon another significant finding which called for further analysis: while 97.3% of the 733 male patients with bronchial carcinomas were smokers, there were 39 nonsmokers among the 59 women with lung cancer, i.e., more than half the female patients. As it was not possible to demonstrate any evidence of special occupational exposure to carcinogens either in the men with lung cancer or in the women -- 47.1% of the women with bronchial carcinomas, being housewives, had no occupation whatsoever, 23.5% were unskilled working women and

17.6% were office workers -- the question arose of what other harmful agents could be considered as being responsible for the especially high percentage of nonsmoking women among our female patients. The fact that general air pollutants play a secondary role as a causative agent of bronchial cancer as well has been shown again just recently by Ulmer [15] in a meticulous study from Northrhine-Westfalia.

Concerning the methods, we refer to our previous publication [5]. Hereditary factors were ruled out already because the great increase in the incidence of bronchial carcinoma in women as well would require a radical change in the hereditary composition in numerous countries in the past decades. Nor is there any indication of such a change [12].

In view of the sensational findings of Hirayama [4] and Trichopoulos et al. [14], we focused our attention primarily on the smoking habits of the husbands and other family members living in the same household with the nonsmoking female lung cancer patients.

A comprehensive review of passive smoking and cancer had been published by Schmidt in MEDIZINISCHE KLINIK in 1979 [9]. In that review he listed, inter alia, more than 40 carcinogenic substances which had been detected in tobacco smoke.

Especially High Carcinogen Level in Sidestream Smoke

The possibility of a cancer-causing effect not only of active smoking but also of passive smoking can no longer be challenged with scientific arguments for the following reasons:

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1. The overwhelming majority of the above-mentioned more than 40 carcinogenic substances present in tobacco smoke enter the surrounding air with the sidestream smoke, and thus the passive smoker is forced to inhale them as well. The sidestream smoke does not differ qualitatively, but only quantitatively from the mainstream smoke which is inhaled by the smoker himself when puffing on the cigarette. Consequently, the health hazard of passive smoking is directly related to the health hazards of the smoker proper. The severe health damage which the "active" smoker must expect makes it ab initio very unlikely for passive smoking to be merely a nuisance. Even though the passive smoker inhales the tobacco smoke in more or less dilute form, the significance of this dilution factor is rendered relative by the fact that the level of the carcinogens among the harmful substances is much higher in the sidestream smoke than in the mainsteam which is inhaled only by the smoker himself.

2. The carcinogenic effect of passive smoking has been clearly established in animal experiments. Ca. 10% of the golden hamsters used developed laryngeal carcinomas even in the experiment designed in the Forschungsinstitut der Deutschen Zigarettenindustrie [Research Institute of the West German Cigarette Industry], and the corresponding percentage was even higher, 20% in a U. S. study. It was possible to increase the lung tumor incidence by passive smoking to 91% in some cases in predisposed mouse strains (reference in [9]).

3. The more than a dozen nitrosamines detected in tobacco smoke deserve particular attention in this respect both qualitatively and quantitatively. One ppm (= parts per million) of them is already

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considered to be potentially carcinogenic. All animal species investigated so far (more than 20) responded to nitrosamine by tumor development without exception. Therefore, we must assume that nitrosamines induce cancer in humans as well.

It is also of particular significance that the nitrosamine level in tobacco smoke is so high that smoking must be considered to be the most important source of exogenous nitrosamine in the environment in general. The situation is further aggravated by the circumstance that according to Brunnemann et al. [1,2], the nitrosamine level in the sidestream smoke is up to 50 times higher than in the mainstream smoke which is inhaled only by the smoker. This especially strongly increased nitrosamine level in the sidestream smoke renders the dilution effect so strongly relative that -- according to the same authors -- the nitrosamine uptake by passive smokers in rooms filled with smoke can reach levels which correspond to the nitrosamine content in the mainstream smoke of up to 30 cigarettes per hour! The nitrosamine level in the sidestream smoke of tobacco is, for example, at least 1,000 times higher than in beer or in aminophenazone, an otherwise good medicine, which was withdrawn from circulation because of minute traces of nitrosamine, or than the maximum values which have been specified recently in the nitrosamine ordinance for pacifiers for babies.

There is No Harmless Dose

4. Carcinogens are distinguished from other toxic substances by their pronounced summation effect. The individual partial doses add up to a critical threshold value beyond which cancer usually

becomes clinically manifest. Even very small doses -- one millionth of one gram -- produce irreversible changes in the cell (= tumor blastoderm). Therefore, in principle, there is no fully harmless dose for carcinogenic substances, because the possibility cannot be ruled out that the partial doses inhaled by passive smoking lead to levels exceeding the carcinogenic threshold value which perhaps would not have been reached otherwise during the life of the patient by summation with other carcinogens present in the environment which none of us can fully escape, and thus cancer becomes clinically manifest during the lifetime. For the same reason, there are no MAC [Maximum Allowable Concentrations] for carcinogenic substances either.

5. **Based on these facts the present epidemiological findings are by no means surprising.** Hirayama's study [4] on more than 91,000 nonsmoking married Japanese women above the age of 40 years should be mentioned in particular in this connection. According to this study, nonsmoking women married to smokers had more than double the lung cancer incidence of women married to nonsmokers. He also found a statistically significant relationship between the lung cancer risk of the nonsmoking women and the intensity of smoking of the spouses, but no such relationship for other forms of cancer (gastric and endometrial cancers).

Similar findings were also obtained by Trichopoulos et al. [14] in Athens by a totally different methodological approach: When comparing the smoking habits of the husbands of 51 women with lung cancer with those of 163 women with other diseases, the lung cancer incidence of nonsmoking women married to smokers was found to increase, on an average,

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by a factor of 2.4, and even by a factor of 3.4 when the husband smoked more than two packs of cigarettes a day.

In a subsequent evaluation of the materials of the prospective study of the American Cancer Society on the pattern of Hirayama's study [4], Garfinkel [3] also found at least a similar tendency, even though it was not possible to demonstrate any statistical significance: When taking the age-adjusted lung cancer incidence in nonsmoking wives of nonsmokers for 1, the figure rose to 1.37 when the nonsmoking women were married to smokers who smoked more than 20 cigarettes a day.

These findings of Garfinkel, which show the same trend as Hirayama's studies, could be plausibly explained when considering the following circumstances: The rooms in Japanese wooden houses, especially in the country, are known to be very small and have low ceilings. Harmful concentrations are reached within a short time due to the small air volume; in agreement herewith the risk for nonsmoking women in the country was especially high. American homes are, however, not only more spacious and the rooms generally bigger, but a higher percentage of them are also air-conditioned. As the homes are bigger, the nonsmoking women in the United States also have more possibility to withdraw to other rooms when they feel excessively bothered by the smoking of their husbands, aside from the tobacco smoke concentration being also generally lower.

Unproportionately High Percentage of Nonsmoking Women with Bronchial Carcinoma Live with Smoking Men

61.5% of the 39 nonsmoking women with bronchial carcinomas in our study lived in the same household with smoking men. This percentage

is far higher than was to be expected based on the percentage of smoking men in the age groups being considered.

The data on the smoking habits were obtained from the family members themselves, usually from the husband, in this study as well. As it was quasi in the interest of these subjects to supply data, they can be assumed to be especially reliable.

According to the recent "microcensus" of the Statistisches Bundesamt [Bureau of Statistics of West Germany] covering 2 million citizens [13], 38.6% of the men were smokers. The majority is accounted for by younger smokers in the age group of 20-40 years. Only 22.4% of the men were smokers in the age bracket 50-69 years, i.e., in the age group which includes most of the husbands of our nonsmoking female patients [6]. When taking this into account, twice or even three times as many of the nonsmoking women with bronchial carcinoma lived together with smoking men than was to be expected statistically, which remarkably duplicates Hirayama's [4] findings in Japan and Trichopoulos' [14] findings in Athens.

The fact that 66.6% of the bronchial carcinomas in the nonsmoking married women were squamous epithelial and small-cell carcinomas is also indicative of the involvement of passive smoking in the development of cancer, because the corresponding percentage was not substantially higher among the smoking women (80%). Since -- as was mentioned before -- occupational exposure to carcinogens and hereditary factors as the cause of the increased incidence of bronchial carcinoma in nonsmoking female patients are ruled out, it could hardly be disputed that the causal involvement of passive smoking in the bronchial carcinomas of the

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nonsmoking married women is by far the most plausible explanation in our study as well.

Sufficient Evidence of Health Hazard

It was demonstrated by Schmidt elsewhere that passive smoking -- completely regardless of a possible carcinogenic effect -- is a true health risk [7,8,10,11]. The exaggerated criticism of the results, especially of Hirayama [4], must therefore be opposed all the more emphatically: The cigarette industry even attempted to make these findings appear incredible in full-page ads in leading newspapers in West Germany. The chief witnesses were, without exception, members of the Forschungsrat Rauchen und Gesundheit der Zigarettenindustrie [Research Council on Smoking and Health of the Cigarette Industry] which distributed 20 million DM made available by the industry for research purposes during the past years without making it public. The inglorious role played by this "Research Council" has already been exposed by one of us elsewhere [10] in detail. With good reason this can be described as no less a scandal than the exposure of the "Neue Heimat". Therefore, the Medical Task Force on Smoking and Health passed the following resolution in its 1981 annual general meeting in Berlin:

"The cigarette industry is increasingly misusing the so-called Research Council on Smoking and Health sponsored by it to manipulate public opinion regarding the question of passive smoking. Therefore, we regard the direct sponsorship of research on the problems of smoking by the cigarette industry and the financial grants, e.g., even to medical journals, bypassing established research institutions, such as the

Deutsche Forschungsgemeinschaft [West German Research Association], as a serious threat to scientific freedom which comes alarmingly close to disguised corruption. Therefore, we urge the West German Federal Minister for Science to guarantee, as a minimum, at least the disclosure by the cigarette industry of how these millions granted for 'promoting research' on smoking are used. In addition, the name of the sponsor should be indicated in all publications of independent institutes on the problem of smoking, which were sponsored by the cigarette industry."

We are pleased to report that von Bülow, West German Federal Minister for Research, has informed the Medical Task Force on Smoking and Health on January 27, 1982 that he considered our demands to be justified -- and not only in this special case -- and that he would take them into account in his further discussions with prof. Schmähl. It is also shameful that leading members of the board of directors of Deutsche Gesellschaft für Arbeitsmedizin [West German Society for Industrial Medicine], e.g., G. Lehnert and H. Valentin, being heavy smokers themselves, do not shrink from turning all principles of preventive medicine upside down and considering passive smoking only as a nuisance until proof of the health hazard, which should be watertight in every respect, is available. According to the principles of preventive medicine, any harmful agent whose health hazards can be supported with an impressive wealth of data as in the case of tobacco smoke in general, should be considered hazardous for health even when diluted until the opposite, i.e., the harmlessness of passive smoking, is proved.

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Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen
Med. Klin. Prax. 78 (1983), Nr. 2

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Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen

Zusammenfassung

In einer Studie an 792 Bronchialkarzinompatienten beiderlei Geschlechts aus dem Raum Mannheim–Ludwigshafen–Heidelberg wurden unter 59 Lungenkrebspatientinnen 39 Nichtraucherinnen gefunden. 61,5% von ihnen hatten in häuslicher Gemeinschaft mit Rauchern gelebt. Das ist nahezu das Dreifache von dem, was aufgrund der Rauchgewohnheiten der Männer in den betreffenden Altersgruppen zu erwarten war. Da Hinweise auf berufliche Kanzerogenexposition ebensowenig ermittelt werden konnten wie erbliche Faktoren, wird das Passivrauchen für den hohen Anteil an Nichtraucherinnen bei unseren Bronchialkarzinompatientinnen als die mit Abstand naheliegendste Erklärung betrachtet, zumal der Anteil an Plattenepithel- und kleinzelligen Karzinomen, die als typische Raucherkrebse gelten, mit 66,6% gegenüber 80% bei den Raucherinnen nicht wesentlich niedriger lag. Als weitere Stütze dieser Interpretation wird auf ähnliche Befunde in der Literatur hingewiesen, die dieses Ergebnis keineswegs als überraschend erscheinen lassen.

In einem vorangegangenen Beitrag (Med. Klin. Prax. 1/1983) waren wir in einer Studie an 792 Lungenkrebspatienten der Frage nachgegangen, ob „Leichtrauchen" (Rauchen von Filterzigaretten) das Lungenkrebsrisiko vermindert, und hatten mindestens fünf Indizien dafür gefunden, daß dies nicht der Fall ist. Dabei stießen wir jedoch auf einen weiteren bedeutsamen Befund, der eine nähere Analyse erforderlich machte: Während 97,3% der 733 männlichen Bronchialkarzinompatienten Raucher waren, fanden sich unter 59 Frauen mit Lungenkrebs 39 Nichtraucherinnen, also mehr als die Hälfte. Da wir Hinweise auf besondere berufliche Kanzerogenexposition weder bei den Männern mit Lungenkrebs noch bei den Frauen ermitteln konnten – 47,1% der Bronchialkarzinompatientinnen übten als Hausfrauen überhaupt keinen Beruf aus, 23,5% waren in ungelernten Berufen tätig und 17,6% waren Angestellte –, ergab sich die Frage, welche weiteren Noxen für den besonders hohen Anteil von Nichtraucherinnen in unserem weiblichen Patientengut in Frage kamen. Daß allgemeine Luftverunreinigungen als Bronchialkrebsursache allenfalls eine Nebenrolle spielen, hat im übrigen Ulmer [15] soeben erneut in einer sorgfältigen Studie aus Nordrhein-Westfalen gezeigt.

Hinsichtlich der Methodik verweisen wir auf unsere frühere Publikation [5]. Erbfaktoren schieden schon allein deshalb aus, weil der starke Anstieg des Bronchialkarzinoms auch bei Frauen eine gravierende Änderung der erblichen Zusammensetzung in zahlreichen Ländern in den letzten Jahrzehnten erfordern würde. Auch dafür liegt kein Anhaltspunkt vor [12].

Im Hinblick auf die aufsehenerregenden Befunde von Hirayama [4] und Trichopoulos et al. [14] wandten wir deshalb unsere besondere Aufmerksamkeit den Rauchgewohnheiten der Ehegatten und anderer in häuslicher Gemeinschaft mit den nichtrauchenden Lungenkrebspatientinnen lebender Angehöriger zu.

Schon 1979 veröffentlichte Schmidt in der MEDIZINISCHEN KLINIK eine umfassende Übersicht über Zwangsrauchen und Krebs [9]. In dieser Übersicht stellte er unter anderem mehr als 40 krebserzeugende Stoffe tabellarisch zusammen, die bisher im Tabakrauch nachgewiesen wurden.

Kanzerogengehalt im Nebenstromrauch besonders hoch

Die Möglichkeit einer krebserzeugenden Wirkung nicht nur des Aktiv-, sondern auch des Passivrauchens läßt sich aus folgenden Gründen mit wissenschaftlichen Argumenten nicht mehr bestreiten:

1. Der größte Teil der erwähnten über 40 krebserzeugenden Stoffe des Tabakrauches geht mit dem Nebenstrom in die Umgebungsluft, wo ihn zwangsläufig auch der Passivraucher einatmen muß. Der Nebenstromrauch unterscheidet sich vom Hauptstromrauch, den der Raucher selbst beim Ziehen an der Zigarette inhaliert, nicht qualitativ, sondern lediglich quantitativ. Das Gesundheitsrisiko des Passivrauchens steht demnach in unmittelbarer Beziehung zu den Gesundheitsgefahren des Rauchens selbst. Schon die schweren Gesund-

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ten einleuchtend erklärt werden: Die Wohnräume in den japanischen Holzhäuschen, speziell auf dem Land, sind bekanntlich sehr klein und niedrig. Durch ihr geringes Luftvolumen werden hier bedenkliche Konzentrationen schon nach kurzer Zeit erreicht; in Übereinstimmung damit war die Gefährdung der nichtrauchenden Ehefrauen auf dem Land besonders hoch. Die amerikanischen Wohnungen sind dagegen nicht nur geräumiger und die Zimmer im Durchschnitt größer, sondern auch in einem hohen Prozentsatz klimatisiert. Durch die größeren Wohnungen hat zudem eine nichtrauchende Ehefrau in den USA, die sich durch das Rauchen ihres Gatten zu stark belästigt fühlt, neben der ohnehin geringeren Tabakrauchkonzentration auch noch eher die Möglichkeit, in andere Wohnräume auszuweichen.

Nichtrauchende Bronchialkrebspatientinnen leben überproportional häufig mit Rauchern zusammen

Von den 39 nichtrauchenden Bronchialkarzinompatientinnen unserer Studie hatten 61,5% in häuslicher Gemeinschaft mit Rauchern gelebt. Das ist weit mehr, als aufgrund des Anteils rauchender Männer in den in Betracht kommenden Altersgruppen zu erwarten war.

Die Angaben über die Rauchgewohnheiten stammten auch hier von den Familienangehörigen selbst, in der Regel vom Ehemann. Da sie quasi in eigener Sache gegeben wurden, darf man annehmen, daß diese Angaben besonders zuverlässig sind.

Nach dem letzten Mikrozensus des Statistischen Bundesamtes an zwei Millionen Bundesbürgern [13] rauchten 38,6% der Männer. Den Hauptanteil stellen dabei die jüngeren Raucher in der Altersgruppe von 20 bis 40 Jahren. Im Alter von 50 bis 69 Jahren – der Altersgruppe, die vorzugsweise als Ehemänner für unsere Patientinnen in Betracht kommt – rauchten sogar nur noch 22,4% der Männer [6].

Stellt man dies in Rechnung, lebten von den nichtrauchenden Bronchialkarzinompatientinnen doppelt oder sogar dreimal so viele mit Rauchern in häuslicher Gemeinschaft, als statistisch zu erwarten war – eine bemerkenswerte Parallele zu den Befunden von Hirayama [4] in Japan und Trichopoulos [14] in Athen.

Für die Beteiligung des Passivrauchens an der Krebsentstehung spricht in unserer Studie auch, daß 66,6% der Bronchialkarzinome bei den nichtrauchenden Ehefrauen Plattenepithel- und kleinzellige Karzinome waren; bei den Raucherinnen waren es mit 80% nicht wesentlich mehr. Da – wie schon erwähnt – berufliche Kanzerogenexposition und Erbfaktoren als Ursachen für das gehäufte Auftreten von Bronchialkrebs bei nichtrauchenden Patientinnen ausscheiden, dürfte kaum zu leugnen sein:

Eine ursächliche Beteiligung des Passivrauchens an den Bronchialkarzinomen der nichtrauchenden Ehefrauen auch unserer Studie ist die mit Abstand einleuchtendste Erklärung.

Gesundheitsschädlichkeit ausreichend bewiesen

An anderer Stelle wurde von Schmidt nachgewiesen, daß das Passivrauchen – völlig unabhängig von einer eventuell krebserzeugenden Wirkung – ein echtes Gesundheitsrisiko darstellt [7, 8, 10, 11]. Mit um so größerem Nachdruck muß deshalb der überspitzten Kritik an den Ergebnissen besonders von Hirayama [4] entgegengetreten werden: Die Zigarettenindustrie versuchte sogar durch ganzseitige Anzeigen in führenden Tageszeitungen der Bundesrepublik Deutschland diese Befunde als unglaubwürdig hinzustellen. Kronzeugen waren dabei ausnahmslos Mitglieder des Forschungsrates Rauchen und Gesundheit der Zigarettenindustrie, der in den letzten Jahren – ohne Offenlegung – 20 Millionen DM an Forschungsmitteln verteilte, die von der Industrie zur Verfügung gestellt wurden. Auf die unrühmliche Rolle dieses „Forschungsrates" ist einer von uns an anderer Stelle [10] im Detail eingegangen. Mit guten Gründen kann man dies als einen nicht minder großen Skandal bezeichnen wie die Enthüllungen um die „Neue Heimat". Schon 1981 verabschiedete deshalb der Ärztliche Arbeitskreis Rauchen und Gesundheit auf seiner Jahreshauptversammlung in Berlin dazu folgende Resolution:

„Die Zigarettenindustrie mißbraucht den von ihr finanzierten, sogenannten Forschungsrat Rauchen und Gesundheit mehr und mehr dazu, die öffentliche Meinung in der Frage des Passivrauchens zu manipulieren. Wir erblikken deshalb in der direkten Forschungsförderung zur Problematik des Rauchens durch die Zigarettenindustrie und in finanziellen Zuwendungen, z. B. auch an medizinische Zeitschriften, unter Umgehung bewährter Forschungseinrichtungen wie der Deutschen Forschungsgemeinschaft, eine ernsthafte Bedrohung der Freiheit der Wissenschaft, die einer getarnten Korruption bedenklich nahekommt. Wir fordern deshalb den Bundeswissenschaftsminister auf, als Minimum eine Offenlegung der Verwendung dieser Millionenbeträge zur ‚Forschungsförderung' über das Rauchen durch die Zigarettenindustrie sicherzustellen. Ferner ist für alle Veröffentlichungen unabhängiger Institute zur Problematik des Rauchens, die durch die Zigarettenindustrie gefördert wurden, ein Hinweis auf den Geldgeber zu fordern."

Erfreulicherweise teilte Bundesforschungsminister von Bülow dem Ärzt-

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heitsschäden, mit denen der „aktive" Raucher rechnen muß, machen es von vornherein höchst unwahrscheinlich, daß das Zwangsrauchen nur eine Belästigung sein *sollte*. Zwar inhaliert der Passivraucher den Tabakrauch mehr oder weniger verdünnt; die Bedeutung dieses Verdünnungsfaktors wird jedoch schon dadurch wesentlich relativiert, daß der Schadstoffgehalt des Nebenstromrauches gerade an Kanzerogenen viel höher ist als der Gehalt im Hauptstrom, den nur der Raucher selbst einatmet.

2. Im Tierexperiment ist die kanzerogene Wirkung des Passivrauchens eindeutig gesichert. Sogar im Forschungsinstitut der Deutschen Zigarettenindustrie selbst entwickelten etwa 10% der verwendeten Goldhamster Kehlkopfkarzinome; nach einer US-Studie waren es sogar 20%. Die Lungentumorrate konnte in disponierten Mäusestämmen durch Passivrauchen zum Teil bis auf 91% gesteigert werden (Literatur bei [9]).

3. Besondere Beachtung verdienen in diesem Zusammenhang die mehr als ein Dutzend im Tabakrauch nachgewiesenen Nitrosamine *sowohl in* qualitativer als auch in quantitativer Hinsicht. Ein 1 ppm (= pars per million) davon gilt bereits als potentiell kanzerogen. Alle – mehr als 20 – bisher untersuchten Tierarten reagierten auf Nitrosamine ausnahmslos mit Tumorbildung. Wir müssen deshalb annehmen, daß Nitrosamine auch beim Menschen Krebs erzeugen.

Von besonderer Bedeutung ist weiterhin, daß gerade der Nitrosamingehalt im Tabakrauch so hoch ist, daß das Rauchen als die wichtigste exogene Nitrosaminquelle in unserer Umwelt überhaupt gelten muß. Erschwerend fällt dabei ins Gewicht, daß der Nitrosamingehalt im Nebenstrom nach Brunnemann et al. [1, 2] bis zu 50mal höher ist als im Hauptstrom, den nur der Raucher selbst einatmet. Durch diese besonders stark erhöhte Nitrosaminmenge im Nebenstrom wird der Verdünnungseffekt so stark relativiert, daß – nach den gleichen Autoren – die Nitrosaminaufnahme von Passivrauchern in stark verqualmten Räumen Werte erreichen kann, die dem Gehalt im Hauptstrom von bis zu 30 Zigaretten stündlich entsprechen! Der Nitrosamingehalt im Nebenstrom des Tabakrauches ist zum Beispiel mindestens tausendfach höher als im Bier oder als im Aminophenazon, einem ansonsten bewährten Medikament, das wegen winziger Nitrosaminspuren aus dem Verkehr gezogen wurde, oder auch als die Höchstwerte, die kürzlich in der Nitrosaminverordnung für Babyschnuller festgelegt wurden.

Eine unschädliche Dosis gibt es nicht

4. Kanzerogene unterscheiden sich von anderen Giften durch ihre ausgeprägte Summationswirkung. Die einzelnen Teildosen addieren sich bis zu einem kritischen Schwellenwert, dessen Überschreitung in der Regel zur klinischen Manifestation des Krebses führt. Schon winzige Dosen – 1 millionstel Gramm reicht dazu schon aus – hinterlassen demnach eine irreversible Veränderung in der Zelle (= Tumorkeimanlage). Eine völlig unschädliche Dosis gibt es deshalb für krebserzeugende Stoffe grundsätzlich überhaupt nicht, weil die Möglichkeit nicht ausgeschlossen werden kann, daß die durch Passivrauchen aufgenommenen Partialdosen durch Summation mit anderen Kanzerogenen in unserer Umwelt, denen sich keiner von uns ganz entziehen kann, dazu führen, daß der krebserzeugende Schwellenwert, der sonst zu Lebzeiten des Patienten vielleicht nicht erreicht worden wäre, durch Vorverlagerung überschritten und somit der Krebs zu Lebzeiten klinisch manifest wird. Aus ebendiesem Grunde gibt es für krebserzeugende Stoffe auch keine MAK-Werte.

5. Legt man diese Gegebenheiten zugrunde, erscheinen die vorliegenden epidemiologischen Untersuchungen keineswegs unerwartet. Besonders ist in diesem Zusammenhang die Studie von Hirayama [4] an mehr als 91 000 nichtrauchenden japanischen Ehefrauen im Alter von mehr als 40 Jahren zu nennen. Nichtraucherinnen zeigten danach eine mehr als doppelt so hohe Lungenkrebsrate, wenn sie mit einem Raucher, statt mit einem Nichtraucher verheiratet waren. Darüber hinaus fand er eine statistisch signifikante Relation des Lungenkrebsrisikos der Nichtraucherinnen zur Intensität des Rauchens des Ehegatten, nicht aber für andere Krebsformen (Magen- und Gebärmutterkrebs).

Gleichsinnige Befunde erhoben auch Trichopoulos et al. [14] in Athen mit einem völlig anderen methodischen Vorgehen: Beim Vergleich der Rauchgewohnheiten der Ehegatten von 51 Patientinnen mit Lungenkrebs mit denen von 163 Frauen mit anderen Krankheiten stieg die Lungenkrebsrate mit einem Raucher verheirateter Nichtraucherinnen im Durchschnitt auf das 2,4fache und – wenn der Ehemann mehr als zwei Päckchen Zigaretten täglich rauchte – sogar auf das 3,4fache.

Zumindest eine gleiche Tendenz – auch wenn sie sich nicht statistisch sichern ließ – fand Garfinkel [3] bei der nachträglichen Auswertung der Unterlagen der Prospektivstudie der American Cancer Society nach dem Muster der Studie von Hirayama [4]: Setzt man die altersberichtigte Lungenkrebsrate nichtrauchender Ehefrauen von Nichtrauchern mit 1 an, stieg sie auf 1,37, wenn die Nichtraucherinnen mit einem Raucher verheiratet waren, der mehr als 20 Zigaretten täglich rauchte.

Diese trendmäßig ähnlichen Befunde von Garfinkel wie in der Untersuchung von Hirayama könnten bei Berücksichtigung folgender Gegebenhei-

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lichen Arbeitskreis Rauchen und Gesundheit am 27. 1. 1982 mit, daß er unsere Forderungen grundsätzlich – und nicht nur in diesem speziellen Fall – für berechtigt hält und sie bei seinen weiteren Diskussionen mit Prof. Schmähl berücksichtigen wird. Beschämend ist auch, daß führende Vorstandsmitglieder der Deutschen Gesellschaft für Arbeitsmedizin, zum Beispiel G. Lehnert und H. Valentin, sich als starke Raucher nicht scheuen, alle Prinzipien der Präventivmedizin auf den Kopf zu stellen, und das Passivrauchen nur als Belästigung gelten lassen wollen, solange keine in jeder Hinsicht hieb- und stichfeste Beweise für die Gesundheitsschädlichkeit vorliegen. Nach präventivmedizinischen Grundsätzen hat jede Noxe, für deren Gesundheitsschädlichkeit ein so erdrückendes Beweismaterial vorgelegt werden kann wie für Tabakrauch prinzipiell, auch bei Verdünnung von vornherein so lange als gesundheitsschädlich zu gelten, bis umgekehrt der Nachweis vorgelegt wird, daß Passivrauchen unschädlich ist.

Summary: Passive smoking as a causal factor of bronchial carcinoma in female non-smokers

In a study on 792 patients with bronchogenic carcinoma of both sexes in the region Mannheim–Ludwigshafen–Heidelberg 59 female bronchogenic carcinomas were found. 39 of them appeared in non–smoking female patients. 61,5% of them had lived in domestic community with smokers. This is nearly the threefold as could be expected on the basis of smoking behavior of men in the respective groups of age. Suggestions on professional exposition to cancerogenic substances could not be found just as little as references to hereditary factors. Passive smoking is by far the obvious interpretation for the high share of non-smokers in our female patients with bronchogenic carcinoma the more so since the percentage of squamous cell and small-cell carcinomas which are valid as typical carcinomas of smokers, did not lie essentially lower in our non-smoking wives (66,6%) in comparison to female smokers (80%). As a further support of this interpretation is refered to similar results in the world literature proving our findings as not surprising.

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Für die Verfasser: Prof. Dr. F. Schmidt, Forschungsstelle für präventive Onkologie, Klinische Fakultät Mannheim der Universität Heidelberg, Maybachstraße 14–16, D-6800 Mannheim 1.

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The risk ratios for passive smoking can be surprisingly high (up to 2 or 3), as reported both by Correa et al and others.[8,9] These risk ratios would be more consistent with those found for active smoking, particularly among women, if the active smoker is at greater risk also from his or her own passive smoke, again through the absorption of radioactivity on the smoke particles passively inhaled; also the relatively higher toxicity of the sidestream smoke[10] might be important.[11] These and other aspects (eg, the urban-rural difference in lung cancer risk from smoking) are more thoroughly discussed elsewhere[12] in the context of indoor radon daughters. Finally, in view of the long latency periods observed among miners acquiring lung cancer from radon daughter exposure,[13] one might suggest that the children of smoking mothers obtain an early exposure to increased levels of radon daughters at home and that smoking later in life promotes the development of lung cancer.

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HANS BERGMAN
OLAV AXELSON

LUNG CANCER AND PASSIVE SMOKING

SIR,—I was surprised to read, in Professor Trichopoulos and colleagues' letter (Sept. 17, p 677), a German study of passive smoking and lung cancer described as having yielded "positive" results. The paper cited[1] contains only tentative conclusions based on poor data analysed by unacceptable methods.

I was also surprised that the findings from the Greek hospital study of passive smoking and lung cancer were almost identical to those reported two years ago[2] despite a substantial increase in the numbers of cases and controls. In the 1981 report the relative risks of lung cancer for non-smoking women were 1, 1·8, 2·4, and 3·4 according to whether their husbands did not smoke, were ex-smokers, or were current smokers of 1–20 or 21 or more cigarettes a day; the updated relative risks are 1, 1·9, 2·4, and 3·4, respectively.

In the 1981 paper the relative risks agreed exactly with the appropriate cross-product ratios calculated from the numbers of cases and controls in the relevant category for husbands' smoking. In the latest results, despite the method being apparently identical, there is a clear disagreement between the relative risks provided by Trichopoulos et al and those I calculate (see table).

RELATIVE RISK OF LUNG CANCER ACCORDING TO SMOKING HABITS OF HUSBAND

Group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)	
			1–20	21+
RR (quoted)	1·0	1·9	2·4	3·4
RR (calculated)	1·0	1·9	1·9	2·5

Relative risk = ratio of risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers.

My calculations suggest that the latest data do not show as clear an association between a woman's lung cancer risk with her husband's smoking habits as the earlier data did. Indeed, relative risks calculated from the additional data are 1, 2·0, 1·8, and 1·8 and do not show the dose-response relation seen earlier. This doubt, added to doubts about the histological evidence and the use of cases and controls from different hospitals (limitations which Trichopoulos et al concede), prompts one to ask if the study really does add to the evidence implicating passive smoking as a factor in lung cancer.

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WOLF-DIETER HELLER

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POTASSIUM CHLORIDE SUPPLEMENTS

SIR,—As your Round the World correspondent predicted,[1] the US Food and Drug Administration advisory committee meeting of March 2 on the controversy of wax-matrix versus microencapsulated potassium chloride preparations proved inconclusive. A few points about this controversy are worth noting.

The study by McMahon et al,[2] showing a favourable result for 'Micro-K' (A. H. Robins) in comparison with 'Slow-K' (Ciba-Geigy) was sponsored by Robins. The study by Patterson et al,[3] showing no difference between micro-K and slow-K, was sponsored by Ciba-Geigy. Both studies have been confirmed by other studies sponsored by the respective company.

Ciba-Geigy, while denying that slow-K is more ulcerogenic than micro-K, has bought from Alfred Benzon Ltd, Denmark, a licence for 'Kalinorm', a microencapsulated (pellet) preparation of KCl similar (or identical) to micro-K. It seems remarkable that Ciba-Geigy is planning to market this preparation when, according to Ciba-Geigy's US subsidiary, "Slow-K has an established clinical record unparalleled by any other solid K supplement".

It seems that, privately, Ciba-Geigy has concluded that kalinorm is as good as micro-K, and that it is better than slow-K, but they would presumably consider it scientifically incorrect to conclude that micro-K is better than slow-K.

Finally I would emphasise, as your RTW correspondent did, that doctors should "re-evaluate the decisive need for a potassium supplement and, if the indication is clear, prescribe it as a liquid". The findings of Patterson et al[3] clearly support this.

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OLLE HANSSON

**This letter has been shown to Dr Burley, whose reply follows.—ED. L.

SIR,—One of the main reasons why slow-release formulations of potassium were developed was the unacceptability of liquid potassium. Indeed, Patterson et al[3] reported that KCP elixir was poorly tolerated in their trial, giving rise to abdominal pain and heartburn in 9 of the 15 volunteers (60%). Dr Hansson omits to mention this. The issue is therefore whether the risk/benefit ratio of 'Slow K' is acceptable. There are eighteen years of clinical experience with slow K in the UK, during which over 4·5 million patient-years of treatment has been prescribed: with 'Micro' K' formulations there is almost no clinical experience. Less than 50 cases of significant alimentary side-effects have been reported with slow K, and some of these were manifestly brought about by previous strictures or oesophageal obstruction due to cardiac enlargement. It would be hard to point to a comparable safety record with any other widely used drug. The fact that a company may be investigating or pursuing alternatives is an indication of interest and involvement in the area, and should not be interpreted as a loss of confidence in an existing product.

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PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK[1]

DALE P. SANDLER, RICHARD B. EVERSON AND ALLEN J. WILCOX

Sandler, D. P. (National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709), R. B. Everson and A. J. Wilcox. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;121:37-48.

Overall cancer risk from adult passive smoking has been examined using smoking by spouse as the measure of exposure. Information on smoking by spouse was obtained for 518 cancer cases and 518 noncancer controls. Cancer cases were identified from a hospital-based tumor registry in North Carolina. Cases included all sites except basal cell cancer of the skin and were between the ages of 15 and 59 years at the time of diagnosis. Cancer risk among individuals ever married to smokers was 1.6 times that [redacted] by confounding by [redacted] social class. [redacted] sites and were not [redacted] tumors. Risks from passive smoking appeared greater among groups generally at lower cancer risk (females, nonsmokers, and individuals younger than age 50 years), but were not limited to these groups.

neoplasms; risk; smoking; tobacco smoke pollution

Passive exposure to cigarette smoke has been linked with a variety of health consequences in humans, including bronchitis and pneumonia in infants (1), reduced pulmonary function (2) and acute respiratory disease in children (3-5), and decreased airway function in otherwise healthy adults (6). Several reports have also focused attention on a possible association between passive exposure to cigarette smoke and lung cancer (7-10).

In a case-control study by Trichopoulos and colleagues (7), 51 white females with lung cancer and 163 controls from an orthopedic service were compared with regard to smoking histories of husbands. Women who were not smokers but were married to smokers were at two- to threefold risk for lung cancer compared with nonsmoking women who were not married to smokers. An updated report of this study involving 77 nonsmoking lung cancer cases and 225 nonsmoking controls confirmed the twofold risk among passive smokers (8). In a prospective study from Japan, Hirayama (9) observed 245 lung cancer deaths among 91,000 married women. The lung cancer death rate for nonsmoking women married to smokers was nearly twice that for nonsmoking women married to nonsmokers and was one-half that for women who themselves smoked. Emphysema was the only other cause of death to exhibit such a pattern, although the trend was not statis-

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tically significant. Most recently, Correa et al. (10) reported a twofold risk for lung cancer among nonsmokers married to smokers. In contrast, analysis of data from an American Cancer Society study in the United States failed to demonstrate an association between passive exposure to cigarette smoke and lung cancer risk (11).

Many of the constituents of mainstream cigarette smoke which is actively inhaled by the smoker are present in reduced quantity in exhaled smoke (12) which is then passively inhaled by the nonsmoker. These same constituents are also contained in sidestream smoke which is released from the cigarette between active puffs and is also inhaled by the passive smoker. One might expect to find, as did Hirayama (9) for lung cancer, that for smoking-related sites, the cancer risk in individuals passively exposed to cigarette smoke might fall between that for smokers and that for nonsmokers. Risk from passive smoking might also be expected to be much lower than that from direct smoking.

However, some chemicals appear in higher concentration in sidestream smoke than in mainstream smoke, making the exposure from passive smoking qualitatively different (12, 13). The health consequences from passive smoking may, therefore, differ from those of direct smoking. These chemicals, many of which are known carcinogens, might lead to increased risk for cancer at sites not shown to be related to direct exposure to cigarette smoke. In comparing sidestream with mainstream smoke, Brunnemann (in refs. 12 and 13) found 52 times as much dimethylnitrosamine, 16 times as much naphthalene, 28 times as much methylnaphthalene, 3.4 times as much benzo(*a*)pyrene, and 5.6 times as much toluene, for example, in sidestream smoke as in mainstream smoke. While the concentrations of these chemicals are higher than in mainstream smoke, actual exposure from passive smoking is heavily influenced by the amount of smoke generated, the volume of ambient air, room ventilation, and the manner in which the cigarettes are smoked.

Differences in the route of inhalation of sidestream and mainstream smoke might also account for differences in site-specific effects. Wynder and Goodman (14), for example, have proposed that if sidestream smoke components are inhaled through the nasal passages, gaseous components but not smoke particulates would reach the lung.

As a preliminary exploration of the hypothesis that passive exposure to cigarette smoke may be carcinogenic, we examined adult passive exposure to cigarette smoke in relationship to cancers of all sites. Since active and passive smokers may differ in the mix of carcinogens to which they are exposed, it is not obvious which sites might be at highest risk of cancer among passive smokers. Since active smokers are also passively exposed, candidate sites might be drawn from those that have been linked with active smoking. However, there may be additional sites whose relationship to smoking has been obscured. In studies comparing smokers with nonsmokers, passive smokers are often included in the nonsmoking group. This would make it difficult to detect small differences in risk due to passive smoking. We report here on cancer risk from passive smoking using smoking histories of spouses as a measure of passive exposure to cigarette smoke during adulthood.

METHODS

Data reported here are from a study of childhood exposure to cigarette smoke and cancer risk in adulthood (29). Cases for study were selected from the hospital-based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between the ages of 15 and 59 years at the time of diagnosis and included all cancer sites e

cept basal cell cancer of the skin. Cases were restricted to this age group to maximize the likelihood of also detecting effects from childhood exposure to cigarette smoke. Individuals older than 60 years in 1981 are not likely to have had mothers who smoked. Patients with multiple primary tumors were included only if the first primary tumor was diagnosed during the study period.

Cases were mailed a questionnaire for self-completion. This mailing was followed by a second mailing and then a telephone call if needed. In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer to serve as comparison subjects. These friends were the same race, sex, and age (±5 years) as the cases. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Beginning with the telephone numbers of the cases, the next higher or lower telephone numbers were called until individuals of the same race, sex, and age (±5 years) were found. For cases interviewed by telephone, the calls to identify controls were made at the same time of day. For cases contacted by mail, telephone controls were chosen during randomly assigned times of day.

Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (15 per cent) either refused ($n = 71$) to participate or could not be contacted. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

Of 518 cases, 360 (70 per cent) named friends or acquaintances who could be contacted as controls. Of these, 86 per cent were successfully contacted for an overall response rate of 60 per cent. To obtain the additional 209 controls, 1,237 households were telephoned. Screening data (age, race, sex, and cancer history of household members) were obtained for 988 households (80 per cent); 224 (23 per cent) of these households had a qualifying member. Fifteen (7 per cent) qualifying telephone controls refused to participate. The overall response rate for selection of telephone controls was 75 per cent (80 per cent × 93 per cent). Although not shown here, data were analyzed separately by control selection group, and the adjusted results were identical to those obtained when the control groups were combined.

Procedurally, the control selection process involved one-to-one matching. This was done to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are for unmatched data to maximize the study sample size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Parallel analyses for matched pairs were carried out. Although not presented here, the results were similar.

Passive exposure to cigarette smoke during adulthood was estimated from a questionnaire report of the number of years of marriage during which a spouse smoked. Subjects were considered exposed if they had a spouse who smoked regularly at any time during their marriage. Regular smoking was defined as smoking at least one cigarette per day for as long as six months. The nonexposed group consisted of persons married to nonsmokers and persons who never married. The quantity smoked was reported as the average number of cigarettes smoked per day by a spouse while married to a study subject.

For the analysis of questionnaire data, odds ratios were calculated, and the chi-square test was used to assess statistical significance. Combined estimates of the odds ratio (OR) in stratified analyses were obtained using the Mantel-Haenszel technique (15). The method of Gart (16) was used to obtain 95 per cent confidence limits

for the combined estimates of the odds ratio. When the 95 per cent confidence limits did not include unity, the odds ratio was considered statistically significant ($p < 0.05$). Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified and adjusted analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, and 50+ years) and three levels of education (<12 years, 12 years, and >12 years).

RESULTS

The distribution of cases by cancer site is shown in table 1. The young age of cases, the referral nature of the hospital, and the fact that the study was limited to living cases account for the distribution of cancers seen. There was a predominance of breast cancers, female genital tract cancers, and leukemia and lymphoma, and a relative lack of respiratory tumors. Eligible cases with respiratory cancer were significantly more likely to die before they could be contacted for this study.

Cases and controls are compared in table 2. Cases and controls are, by design, distributed similarly by race and sex, with 70 per cent of each group white and 67 per cent female. The mean age of cases (43.6 years) and controls (43.5 years) is also similar. Level of education differs significantly between groups; 45 per cent of cases and 36 per cent of controls never graduated from high school. Level of education, therefore, is taken into consideration in most analyses. On the other hand, cases and controls do not differ by broad occupational category. A greater proportion of controls never married (16 per cent vs. 13 per cent), but this difference is not statistically significant. Cancer cases and controls also do not differ in reported smoking histories. In part this is due to the relative absence of lung cancer cases and to the method of control selection. Sixty per cent of controls are friends of cases, and the smoking habits of individuals who are friends may be similar. When only cases with population controls are included, 57 per cent of cases and 46 per cent of population controls were smokers.

[redacted] (table 3). Adjusting independently

TABLE 1

Distribution of cancer cases by site of primary tumor and study status

Site	ICD† No.	Included		Refused or lost	
		No.	(%)	No.	(%)
Lip, oral cavity, and pharynx	140–149	22	(4)	15	(7)
Digestive organs and peritoneum	150–159	41	(8)	16	(7)
Respiratory and intrathoracic organs	160–165	32	(6)	43	(19)*
Bone, connective tissue, and skin	170–173	42	(8)	13	(6)
Breast	174	60	(12)	16	(7)
Female genital organs	179–184	175	(34)	61	(28)
Prostate	185	10	(2)	0	(0)
Testis	186	6	(1)	3	(1)
Urinary tract	188, 189	6	(1)	9	(4)
Eye, brain, and other nervous system	190–192	38	(7)	20	(9)
Thyroid and other endocrine glands	193, 194	27	(5)	3	(1)
Lymphatic and hematopoietic tissue	200–207	52	(10)	13	(6)
Site unspecified	199	7	(1)	10	(5)
All sites		518	(100.0)	222	(100.0)

* $p < 0.01$.

† ICD, *International Classification of Diseases*, Ninth Revision.

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TABLE 2
Comparison of cases and controls

Factor	Cases No. (%)	Controls No. (%)
Total	518 (100)	518 (100)
Age		
<30	96 (19)	99 (19)
30–39	89 (17)	105 (20)
40–49	132 (25)	121 (23)
50+	201 (39)	193 (37)
Race		
Nonwhite	153 (30)	153 (30)
White	365 (70)	365 (70)
Sex		
Male	169 (33)	169 (33)
Female	349 (67)	349 (67)
Marital status*		
Never married	65 (13)	79 (16)
Ever married	444 (87)	410 (84)
Education†		
<12 years	233 (45)	186 (36)
12 years	137 (27)	186 (36)
>12 years	147 (28)	146 (28)
Occupation‡		
Blue collar	172 (35)	194 (38)
White collar	192 (39)	175 (34)
Housewife	118 (24)	131 (26)
Unemployed	8 (2)	11 (2)
Smoking		
Never	235 (45)	247 (48)
Ever	283 (55)	271 (52)
Current	154 (30)	166 (32)
Past	129 (25)	105 (20)

* Nine cases and 29 controls did not report marital status.

† One case did not report years of education.

‡ Twenty-eight cases and seven controls did not report occupation.

and in combination for sex, age, race, smoking, parental smoking, education, and occupation does not change this finding. Cancer risk from passive exposure to cigarette smoke appears greatest for females and for individuals who are not themselves smokers, with statistically significant risks limited to these subgroups. There are no apparent subgroup differences in risk with race or occupational category (blue collar or white collar), although risk appears greater for individuals with at least a high school education. Cancer risk in relationship to passive exposure to cigarette smoke also appears limited to individuals who are younger than age 50 years.

Cancer risks from passive smoking among smokers and nonsmokers are shown separately in table 4. Risk is clearly elevated among nonsmokers, with the twofold risk significant after adjustment for age, race, or sex. Risk is also elevated among smokers, but the 30 per cent increase in risk is only of borderline statistical significance. Among nonsmokers, risk does not differ with race, but the risk from passive exposure is statistically significant only among females and among individuals between the ages of 30 and 49 years, although it is also elevated for males. For smokers, risk is significantly elevated among females and whites. The twofold risk related to passive exposure among individuals younger than 30 years (table 3) is due to risk among individuals who are themselves smokers (OR = 2.3) (table 4). The lower risk among nonsmokers in this age group (OR = 1.4) contrasts with the greater risk among nonsmokers in the other age categories under age 50 years. This suggests that the cumulative exposure through passive means alone, for this young group may be below that which would pose a risk.

For most cancer sites, the number of cases is too small for meaningful site-specific analysis. However, statistically significant risks in relationship to passive smoking are seen for breast cancer, cervical cancer, and endocrine cancers. Odds ratios adjusted for possible differences in the distributions of age and level of education are shown in table 5 for smokers and nonsmokers combined.

The twofold risk of breast cancer shown in table 5 is not substantially changed by adjustment for education, race, age, smoking status, or parental smoking. Breast cancer risk is greater among younger women (OR = 3.4 for women <50 years vs. OR = 1.1 for women ≥50 years) and those with at least a high school education (OR = 3.3 vs. OR = 1.0).

The twofold risk for cervical cancer

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TABLE 5

Overall cancer risk from smoking by spouse, adjusted separately† for potential confounding factors

Factor	% exposed‡		Crude OR†	Adjusted OR	95% CL† on adjusted OR
	Cases§ (n = 508)	Controls (n = 489)			
Crude risk	55	43	1.6**		(1.3, 2.1)
Sex					
Male	35	26	1.5**		
Female	65	51	1.[illegible]**	1.7**	(1.3, 2.2)
Age					
<30	39	24	2.0*		
30–39	55	39	1.9*	1.6**	(1.3, 2.1)
40–49	67	47	2.2**		
50+	56	54	1.2		
Race					
Nonwhite	50	34	1.6*		
White	58	45	1.7**	1.6**	(1.3, 2.1)
Smoking					
Nonsmokers	52	34	2.1**		
Smokers	58	51	1.3	1.6**	(1.3, 2.1)
Education					
<12 years	55	52	1.1		
12 years	61	35	2.9**	1.6**	(1.2, 2.1)
>12 years	50	41	1.5		
Occupation¶					
Blue collar	53	40	1.7*		
White collar	53	40	1.7*	1.7**	(1.2, 2.3)
Either parent smoked					
No	55	41	1.8**	1.8**	(1.3, 2.3)
Yes	57	44	1.7**		

* $p < 0.05$.

** $p < 0.01$.

† OR, odds ratio, after multiple adjustment for age, race, sex, education, and smoking status = 1.7, 95% confidence limits (CL) = (1.3, 2.3).

‡ Spouse ever smoked while married to study subject.

§ Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

¶ Excludes housewives, those unemployed, and those missing data on occupation.

among individuals passively exposed to cigarette smoke is also not affected by adjustment for age, race, smoking status, or smoking by parents. The estimated risk is reduced somewhat by adjustment for level of education, but there is no clear pattern of risk with level of education. As for the other sites, risk appears greatest among younger women (OR = 2.9 for women <50 years vs. OR = 0.9 for women ≥50 years). Odds ratios are statistically significant for whites and for nonsmokers, but the magnitude of the risks for nonwhites and for smokers is similar.

There is also a statistically significant risk of endocrine tumors among exposed individuals, which remains after adjustment for potential confounding variables. In subgroup analyses, risk is significant for younger individuals, nonsmokers, individuals with a high school education, and individuals whose parents did not smoke.

Although the number of lung cancer cases is small (n = 22), lung cancer risk from passive exposure to cigarette smoking is examined in table 6 because of current interest in this site. The overall crude risk of 1.9 is not statistically significant. However, the odds ratios for females (OR = ∞) and for nonsmokers (OR = ∞) are statisti-

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TABLE 4

Overall cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers, adjusted for potential confounding factors

Factor	Nonsmokers (n = 466)				Smokers (n = 532)			
	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)
	No. (% exposed)	No. (% exposed)			No. (% exposed)	No. (% exposed)		
Crude risk	231 (52)	235 (34)	2.1**		278 (58)	254 (51)	1.3	
				(1.4, 3.0)				(0.9, 1.9)
Age								
<30	45 (22)	58 (17)	1.4		50 (54)	38 (34)	2.3	
30–39	36 (56)	49 (31)	2.8*	2.0**	51 (55)	48 (48)	1.3	1.4
40–49	63 (68)	48 (33)	4.3**	(1.4, 2.9)	67 (64)	66 (58)	1.3	(1.0, 1.9)
50+	87 (53)	80 (49)	1.2		110 (58)	102 (55)	1.1	
Sex								
Male	39 (13)	57 (9)	1.5	2.0**	128 (41)	102 (36)	1.2	1.5*
Female	192 (59)	178 (42)	2.0**	(1.3, 2.9)	150 (73)	152 (61)	1.7*	(1.0, 2.1)
Race								
Nonwhite	72 (53)	83 (31)	2.5**	2.0**	77 (47)	63 (48)	1.0	1.4
White	159 (51)	152 (36)	1.9**	(1.4, 3.0)	201 (63)	191 (52)	1.5*	(1.0, 1.9)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for spouse smoking.

‡ OR, odds ratio.

§ CL, confidence limits.

cally significant even though they are based on small numbers. Since only two lung cancer cases were nonsmokers and only seven were females, it is not possible to examine lung cancer in greater detail. Risk is also elevated among younger individuals and among those with at least a high school education.

Among nonsmokers alone, risks were significantly elevated for endocrine and cervical cancer, despite the loss of power from reducing the already small number of cases for site-specific analysis (table 7). The twofold risk for breast cancer seen overall is also seen for nonsmokers but is not quite statistically significant. Among smokers, the odds ratio is statistically significant for breast cancer only. However, the approximately twofold risk for cervical cancer is similar to that among nonsmokers.

There is no clear dose-response relationship for all cancer sites combined or for specific sites in relationship to either the number of years married to a smoker (adjusted for age) or the average number of cigarettes smoked per day. This is true for smokers and for nonsmokers and also when analysis is confined to those younger than age 50 years, to whom an effect of passive smoking appears limited.

DISCUSSION

We have found a significantly elevated overall cancer risk for individuals passively exposed to cigarette smoke. This cannot be readily explained by a number of other factors, including individual smoking habits and two measures of social class: education and broad occupational category. Elevated risks were seen for several specific cancer sites and were not limited to lung cancer or other "smoking-related" tumors. These findings might relate to other factors we have not measured or to deficiencies in study design. However, we have not been able to identify a possible confounder or a bias of selection or recall that could have caused the difference in smoking patterns of spouses between cases and controls. Study subjects and interviewers were told

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TABLE 5

Cancer risk from passive exposure to cigarette smoke, adjusted for age and education, all sites combined and specific sites

Site	Cases No.† (% exposed)‡	Crude OR§	Adjusted OR§	95% CL∥ on adjusted OR§
All sites	508 (55)	1.6**	1.6**	(1.2, 2.1)
Lip, oral cavity, and pharynx	22 (55)	1.6	1.1	(0.4, 3.0)
Digestive system	39 (51)	1.4	1.0	(0.5, 2.2)
Respiratory system	32 (50)	1.3	1.0	(0.5, 2.4)
Lung	22 (59)	1.9	1.5	(0.6, 4.3)
Bone, connective tissue, and skin	42 (36)	0.7	0.7	(0.3, 1.5)
Breast¶	59 (69)	2.2**	1.8*	(1.0, 3.7)
Female genital system¶	170 (66)	1.9**	1.8**	(1.2, 2.8)
Cervix	101 (67)	2.0**	1.8*	(1.1, 3.2)
Prostate¶	10 (30)	1.2	0.8	(0.1, 3.9)
Testis¶	5 (40)	1.9	2.6	(0.2, 49.9)
Urinary tract	6 (50)	1.3	1.1	(0.2, 7.6)
Eye, brain, and other nervous system	38 (32)	0.6	0.7	(0.3, 1.5)
Endocrine	26 (65)	2.5*	3.2**	(1.4, 9.4)
Hematopoietic	52 (44)	1.1	1.3	(0.7, 2.5)
Other	7 (57)	1.8	1.8	(0.3, 10.4)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

‡ For comparison, 210 of 489 controls (43%) were exposed.

§ OR, odds ratio.

∥ CL, confidence limits.

¶ Sex-specific comparison. Of 330 female controls, 51% were exposed. Of 159 male controls, 26% were exposed.

simply that the study was designed to look at smoking patterns in families.

Cases and controls were similar with regard to their own smoking histories. This was partly because of the choice of friend controls who tended to have similar smoking histories and because known smoking-related sites were underrepresented in the case population. Cases included in the study were generally younger than those with smoking-related tumors. Unavoidable delays between case identification and completion of interviews also contributed to the lack of smoking-related cancers. Persons with lung cancer and other smoking-related tumors were more likely to have died before they could be interviewed. In addition, because of the special interests of physicians at the hospital from which cases were identified, breast cancers and gynecologic cancers were overrepresented. As a result of this unintentional matching on smoking status, risks from passive smoking and direct smoking cannot be compared.

The route of exposure for the passive smoker is via inhalation. Reports of effects on upper respiratory tract function (2–6) are consistent with this. There has also been a report of mutagens measured in the urine of passive smokers (17), indicating that components of cigarette smoke enter the bloodstream and are circulated throughout the body of the passive smoker. Another report indicated that enzyme activity can be induced by passive exposure to cigarette smoke (18). These findings are tentative, but do suggest that an overall increase in cancer risk or an increase in risk for specific nonrespiratory sites following passive exposure to cigarette smoke is plausible.

TABLE 6

Lung cancer risk from passive exposure to cigarette smoke, adjusted for potential confounding factors

Factor	Cases No. (% exposed)	Crude OR†	Adjusted OR†	95% CL‡ on adjusted OR†
Crude risk	22 (59)	1.9		(0.8, 5.0)
Sex				
Male	15 (40)	1.9		(1.1, 8.4)
Female	7 (100)	∞**	3.4*	
Smoking				
Nonsmokers	2 (100)	∞*		
Smokers	20 (55)	1.2	1.5	(0.6, 3.9)
Age				
<50	5 (80)	6.7		
50+	17 (53)	1.0	1.5	(0.6, 3.8)
Education				
<12 years	15 (47)	0.8		
12 years	4 (100)	∞**	1.6	(0.6, 4.4)
>12 years	3 (67)	2.8		
Either parent smoked§				
No	6 (50)	1.5	1.5	(0.5, 4.8)
Yes	9 (56)	1.6		

* $p < 0.05$.
** $p < 0.01$.
† OR, odds ratio.
‡ CL, confidence limits.
§ Numbers reduced because of missing data on parental smoking.

TABLE 7

Cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers: selected sites

Site	Nonsmokers No. of cases	Nonsmokers Odds ratio	Nonsmokers (95% CL†)	Smokers No. of cases	Smokers Odds ratio	Smokers (95% CL†)
Lung	2	∞‡		20	1.2	(0.5, 2.9)
Breast	32	2.0	(0.9, 4.3)	27	2.8*	(1.0, 7.6)
Cervix	56	2.1*	(1.2, 3.9)	45	2.0	(0.9, 4.1)
Endocrine glands	13	4.4*	(1.2, 17.4)	13	1.5	(0.4, 5.5)

* $p < 0.05$.
† CL, confidence limits.
‡ $p = 0.051$.

Our study was intended to consider a range of effects similar to what might be measured in a prospective study of a cohort of individuals who are passively exposed. Such an approach serves to single out sites which appear to be important as well as to investigate whether passive exposure might increase susceptibility to additional insults, thereby increasing cancer risk overall. Two reports in the literature use prospectively collected data (9, 11). One of these (11), however, does not provide data on cancer risks at sites other than the lung, and neither report provides data on overall cancer risk from passive exposure to cigarette smoke. Data from the Japanese study recently presented by Hirayama, however, indicate that cancer risk may be increased at sites other than the lung and that risk may not be limited to smoking-related sites (Hirayama, personal communication: presented at Hawaii Cancer Conference, 1984).

For this study, passive exposure during adult life is determined from a question-

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naire report of the number of years of married life during which a spouse smoked. Misclassification of exposure status is likely for individuals who never married but have lived with other persons who smoked. Slightly more controls than cases reported never marrying, which might lead to differential misclassification. However, we reanalyzed our data, excluding subjects who never married, and found the results to be the same. When only married subjects were included, the odds ratio for cancers of all sites combined was also 1.6. We made no allowances for multiple spouses, other members of the household who smoke, or passive exposures which occur outside of the home. Quantity smoked, too, is an approximate measure. The reported number of cigarettes smoked per day by the spouse is simply the average daily amount smoked during that time period. No allowance was made for changes in smoking habits of the spouse over time or for time since last exposure if the spouse did not smoke during the entire married interval.

Nonetheless, we found smoking by spouse to be significantly associated with overall cancer risk. The odds ratio of 1.6 was not substantially altered by adjustment for age, race, sex, smoking status, education, or occupation. Risk was limited to individuals younger than age 50 years, who were at approximately twofold risk. Risk was also greatest for females and nonsmokers, although not entirely limited to these groups.

When smokers and nonsmokers are considered separately, the twofold risk among nonsmokers is highly significant and is not altered by adjustment for potential confounding factors. The 30 per cent increase in risk among smokers whose spouses also smoke is only of borderline statistical significance, but is also unchanged by adjustment for other factors. The groups for whom risk from passive smoking appeared greatest are those groups generally at lower cancer risk overall. It may be that the small risk imposed by passive exposure during adult life is difficult to detect statistically in individuals at risk from other causes. Also, women who smoke may tend to smoke less, start later, and inhale differently than men. This would allow for a greater impact of passive exposure among women, regardless of their own smoking status. In addition, very few nonsmoking men are married to smokers, making it more difficult to detect a risk among males. In our data, only 10 per cent (10/96) of nonsmoking males were married to smokers, whereas 51 per cent (189/370) of nonsmoking females were married to smokers.

The increased cancer risk from passive exposure was not limited to sites generally thought to be smoking-related (12, 13). In fact, because of our case selection procedures and delays in interviewing cancer cases, individuals with cancers of smoking-related sites were only a small proportion of total cases. If cancers of the esophagus, respiratory tract, oral cavity and pharynx, urinary tract, and pancreas are designated smoking-related, the odds ratio for smoking-related tumors is 1.3, whereas the odds ratio for other sites is 1.7 ($p < 0.01$). Evidence is accumulating that cancer of the cervix should also be included among those sites that are smoking-related (19–21). When the cervix is included, the odds ratio for smoking-related sites is 2.0 and for other sites is 1.5, both of which are statistically significant.

Only 22 lung cancer cases are included in this report, with an odds ratio of 1.9 among passive smokers. Although not statistically significant, it is consistent with the level of risk reported in other studies. For women and for nonsmokers, the risk of lung cancer among those passively exposed was significantly increased despite very small numbers. The odds ratio for individuals under age 50 years was of borderline significance. Hirayama (9) reported a twofold risk for women married to smokers and found that risks were also greatest among younger women (as measured by husband's age). While Garfinkel (11) didn't find an

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overall relationship of passive exposure to lung cancer risk, the relative risk among women married to smokers was in the same direction. Relatively few women in Garfinkel's cohort were under age 50 years, which might explain these inconsistent results.

In a study reported by Correa et al. (10), a twofold relative risk was seen among nonsmokers married to smokers. The risks were similar for males and females, although the number of nonsmoking males with lung cancer was very small. Among smokers, males who were light smokers with wives who were heavy smokers had a relative risk of 1.5. Trichopoulos et al. (7, 8) also reported an overall twofold lung cancer risk which was statistically significant among nonsmoking women married to smokers.

The studies reported by Trichopoulos et al. (7, 8), Correa et al. (10), and Hirayama (9) all suggest a dose-response relationship, although different measures of dose were employed in the three studies. In our study, there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose, but the number of lung cancer cases may be too small to expect a consistent trend. Evaluation of dose is not straightforward and depends on factors which we did not measure, such as room ventilation and smoking "style" of the spouse.

We found a twofold cervical cancer risk, which persisted after adjustment for level of education, among women whose husbands smoked. We did not collect data on sexual activity of cases or spouses. We also see an increased risk of breast cancer. Since the sociodemographic risk factors for these two sites are not the same, this supports the conclusion that the apparent excess cervical cancer risk is not entirely due to confounding by social class. Buckley et al. (22) reported a fourfold risk of cervical cancer among women whose husbands smoked, but after adjustment for number of sexual partners of the husband, the resulting twofold relative risk was not significant. Similar results were reported by Brown et al. (23). Hirayama (9) did not find elevated cervical cancer risk among women whose husbands smoked. This may relate to differences in the ages of the women studied or to differences in risk from other factors.

No previous study has reported a positive association between breast cancer and either passive or direct exposure to cigarette smoke (24–26). In a recently reported study by Rosenberg et al. (27), the relative risk for breast cancer was approximately 1.0 for exsmokers, current smokers, and heavy smokers as compared with nonsmokers. The crude odds ratio of 2.2 that we report is not reduced by adjustment for a number of potential confounding variables. Risk is not seen among women older than age 50 years or among women with less than a high school education, but is fairly constant across all other groups. Petrakis (28) has detected nicotine in breast fluid of nonlactating women who smoked, which may lead to alterations in breast tissue. This would support a possible role for passive smoking if passive exposure also caused such an effect.

One other site for which we find an association with passive exposure, endocrine glands, is not generally thought to be smoking-related. The number of tumors here is small, of which 11 are thyroid tumors.

In summary, passive exposure to smoking by spouse is related to an overall risk of cancer in our data. This association persists after adjusting for possible confounding factors. Associations with several specific tumor sites are also statistically significant, including some which are not ordinarily regarded as smoking-related. Further studies are required to confirm this broad spectrum of carcinogenicity by passive smoking and to explore the unexpected site-specific findings.

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Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking

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Abstract: We obtained data on smoking by parents from 438 cancer cases and 470 controls to investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke. Cancer cases were between ages 15 and 59 at time of diagnosis. All sites but basal cell cancer of the skin were included. Cancer risk was increased 50 per cent among offspring of men who smoked. Increased risk associated with father's smoking was not explained by demographic factors, social class, or individual smoking habits, and was not limited to known smoking related sites.

Relative risk (RR) estimates associated with father's smoking tended to be greatest for smokers, males, and non-Whites. There was only a slight increase in overall cancer risk associated with maternal smoking. Mother's and father's smoking were both associated with risk for hematopoietic cancers, and a dose-response relationship was seen. The RR for hematopoietic cancers increased from 1.7 when one parent smoked to [illegible] when both parents smoked. Although they should be considered tentative, study findings suggest a long-term hazard from transplacental or childhood passive exposure to cigarette smoke. (*Am J Public Health* 1985; 75:487–492.)

Introduction

Cancer risk in adult life may be affected by transplacental and childhood exposure to cigarette smoke.[1] Data from studies in animals have demonstrated that many carcinogens are active when administered transplacentally or during early life. In some instances, effects may be produced at lower doses than are required for adults.[2-6] The tumors resulting from these transplacental and early postnatal exposures may not be apparent until adulthood.[3,7-9]

Studies in humans demonstrate that the fetus of smoking parents is exposed to components of cigarette smoke and is capable of bioactivating these chemicals.[10-20] For example, cotinine has been measured in the amniotic fluid of smokers and passive smokers[13] and thiocyanate has been measured in fetal cord blood.[14-16] Studies have also demonstrated increased activity of enzymes that metabolize benzo(a)pyrene in placentas of women who smoke,[17-19] and possibly even in placentas of women passively exposed to cigarette smoke.[20] Similar elevations may occur in the tissues of the fetus or exposed child. Finally, increased urinary excretion of mutagens has been found in passive smokers.[21]

Several epidemiologic studies have demonstrated increased risk for childhood tumors in relation to either paternal or maternal smoking,[22-24] but not all studies demonstrate an increased risk.[25,26] Even if no increased risk of childhood cancer were found, however, it would not rule out the possibility of increased cancer risk during adult life from fetal or childhood exposure. One recent study found elevated lung cancer risk for individuals whose mothers smoked.[27]

Cigarette smoke contains many known carcinogens.[28] Sidestream smoke, which is the smoke released from the cigarette between active puffs, may differ qualitatively from the mainstream smoke which is inhaled by the active smoker.[28] Some compounds occur in markedly higher concentrations in sidestream smoke, and although this smoke is diluted by the ambient air into which it is released, the passive smoker may inhale smoke which is qualitatively richer in certain compounds than mainstream smoke (Hoffman in 28). For example, the concentration of dimethylnitrosamine in sidestream smoke is 52 times that in mainstream smoke. Such qualitative differences make it difficult to predict the biologic effect of exposure to sidestream smoke.

In this study we investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke.

Methods

Our study methods have been described in greater detail elsewhere.[29] Cancer cases were selected from the hospital based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between ages 15 and 59 at time of diagnosis and included all cancer sites except basal cell cancer of the skin. Cases were restricted to age 59 and younger, since fewer than 5 per cent of women of child bearing age in 1920 were smokers.[30,31]

Cases were mailed a questionnaire for self completion, followed by a second mailing and a telephone call if needed. Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (16 per cent) either refused (n = 71) to participate or could not be contacted. Cases who died or did not respond were slightly older and were more often male or non-White; cases with respiratory cancer were more likely to have been excluded, presumably due to higher case fatality. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer and were the same race, sex, and age (± 5 years) to serve as comparison subjects. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Data were analyzed separately by control selection group and the adjusted results were nearly identical to those obtained when the control groups were combined.

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Individuals were specifically requested to supply information on natural parents. Only individuals who lived with both natural parents for all or most of the first 10 years of life are included in this report. As a result, 128 individuals were excluded (80 cases and 48 controls).

Transplacental and childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents. Subjects were asked whether parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the study subject. Subjects were also asked the usual quantity of cigarettes smoked by the parents and the frequency of smoking in the house. For this report, unless otherwise specified, exposure is classified by parental smoking in the household before the subject attained 10 years of age.

For this report, "smoking related" tumors were defined as cancer of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix.[23] Because evidence linking cervical cancer with cigarette smoking is not well documented, we also analyzed these data with cervical cancer excluded from this designation. The number of "smoking related" tumors was substantially reduced by this exclusion, but the general findings were not altered. For individual smoking status, smokers are defined to include anyone who ever smoked at least one cigarette a day for as long as six months. Nonsmokers are individuals who have never smoked.

Estimates of the relative risk (RR) in stratified analyses were obtained using the Mantel-Haenszel technique[32] for the summary odds ratio. The method of Gart[33] was used to obtain 95 per cent confidence limits for the combined estimates of RR. Estimates of the relative risk adjusted simultaneously for multiple confounding variables were obtained using a multiple logistic model.

Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, 50+) and three levels of education (<12 years, 12 years, >12 years). Age was treated as a continuous variable in the multiple logistic analysis.

Controls were matched one-to-one to cases to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are unmatched to maximize the study size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Analyses using matched pairs gave similar results.

Results

Cases and controls are distributed similarly by age, race, and sex (Table 1). Cases and controls differ only in their distribution by years of schooling with fewer cases having completed high school. However, cases and controls are similar in broad occupational categories. Cases and controls are similar with regard to their own smoking status with 45 per cent of cases and 47 per cent of controls never having smoked; the similarity is largely due to the use of friends as controls. When only cases with population controls are included, 57 per cent of cases and 47 per cent of population controls were smokers.

Maternal Smoking

There was only a small difference between cases and controls in reported exposure to maternal smoking [estimated relative risk (RR) = 1.1, 95 per cent confidence limits = 0.7, 1.6]. The RR for cancer among individuals whose mothers smoked was close to one for all measures of maternal smoking, and this lack of association persisted after adjustment for potential confounding factors including age, race, sex, education, individual smoking, and method of control selection.

Site specific relative risk estimates were calculated for 13 different sites, even though for many sites the number of cases is too small for detailed analysis. For most sites, the RR in relation to maternal smoking was close to one (Table 2). However, the RR for leukemia and lymphoma was 2.7 (95 per cent confidence limits = 1.3, 5.8). The RR for hematopoietic cancers associated with maternal smoking is greater for individuals whose fathers also smoked (2.6 vs 1.5 for nonsmoking fathers), but the RR remained elevated (RR = 2.4, 95 per cent confidence limits = 1.0, 5.5) after adjusting for father's smoking. Adjustment for age, race, sex, education, and individual smoking did not change this finding. The numbers of specific hematopoietic cancers are small precluding detailed analysis. However, the crude RR for Hodgkins disease (RR = 4.4, 95 per cent confidence limits = 1.1, 4.6), non-Hodgkins lymphomas (RR = 1.7, 95 per cent confidence limits = 0.5, 5.2) and acute leukemias (RR = 8.8, 95 per cent confidence limits = 2.0, 40.0) were greater than one.

TABLE 1—Comparisons of Cases and Controls

Factor	Cases N (%)	Controls N (%)
Total	438 (100)	470 (100)
Age (years)		
<30	83 (19)	89 (19)
30–39	72 (16)	95 (20)
40–49	117 (27)	110 (23)
50–59	166 (38)	176 (37)
Mean Age	43	43
Race		
White	325 (74)	340 (72)
Non-White	113 (26)	130 (28)
Sex		
Male	147 (34)	158 (34)
Female	291 (66)	312 (66)
Education†		
<12 years	182 (42)	164 (35)
12 years	122 (28)	171 (36)
>12 years	133 (30)	135 (29)
Occupation†		
Blue Collar	158 (39)	154 (34)
White Collar	154 (38)	183 (40)
"Housewife"	97 (24)	118 (26)
Smoking Status		
Nonsmoker	197 (45)	223 (47)
Smoker	241 (55)	247 (53)
Mother's Smoking†		
No	353 (84)	389 (85)
Yes	65 (16)	66 (15)
Father's Smoking†		
No	166 (44)	234 (53)
Yes	212 (56)	204 (47)

†Numbers reduced because of missing values.

TABLE 2—Cancer Risk from Mother's Smoking, All Sites Combined and Selected Sites

Site	Cases No.	Cases (% exposed)†	Crude RR	95% Conf. limits
All Sites	418*	(16)	1.1	(0.7, 1.6)
"Smoking Related"	131	(13)	0.9	(0.5, 1.6)
Not "Smoking Related"	287	(17)	1.2	(0.8, 1.8)
Lip, Oral Cavity and Pharynx	17	(12)	0.8	(0.2, 3.5)
Digestive System	31	(10)	0.6	(0.2, 2.1)
Respiratory System	22	(14)	0.9	(0.3, 3.2)
Lung	15	(13)	0.9	(0.2, 4.1)
Bone, Skin and Connective Tissue	36	(8)	0.5	(0.2, 1.8)
Breast‡	53	(15)	0.9	(0.4, 2.1)
Female Genital Tract‡	103	(17)	1.1	(0.7, 2.2)
Cervix‡	80	(15)	0.9	(0.6, 1.9)
Prostate§	10	(0)	0.0	(0.0, 3.7)¶
Testis§	5	(20)	1.8	(0.2, 16.6)
Urinary Tract	6	(0)	0.0	(0.0, 5.1)¶
Eye, Brain and Other Nervous System	37	(11)	0.7	(0.2, 2.1)
Brain	31	(13)	0.9	(0.3, 2.7)
Endocrine Glands	21	(19)	1.4	(0.5, 4.2)
Hematopoietic Tissue	41	(32)	2.7	(1.3, 5.8)
Other	6	(17)	1.2	(0.1, 10.3)

*Missing values for mother's smoking
†For comparison 66 (15%) of 455 controls were exposed to mother's smoking
‡Sex specific comparison: 16% of 301 female controls were exposed
§Sex specific comparison: 12% of 154 male controls were exposed
¶Exact confidence limits

Paternal Smoking

There was an overall relative risk estimate of 1.5 (95 per cent confidence limits = 1.1, 2.0) for cancer among individuals whose fathers smoked in the household (Table 3). Adjusting for potential differences in age, sex, race, individual smoking status, smoking by spouse, education, maternal smoking, or method of control selection did not alter this finding (RR = 1.5). Estimates of the adjusted RR were obtained separately for the group with friend controls (RR = 1.6) and the group with population controls (RR = 1.4). The combined adjusted RR in a matched pairs analysis with a much smaller data set was also similar. The RR for cancer associated with father's smoking was greater for males than females (1.7 vs 1.4), for non-Whites than for Whites (1.7 vs 1.4), and for smokers than for nonsmokers (1.7 vs 1.2).

TABLE 3—Cancer Risk from Father's Smoking, All Sites Combined and Selected Sites

Site	Cases No.	Cases (% exposed)†	Crude RR	95% Conf. limits
All Sites	378*	(56)	1.5	(1.1, 2.0)
"Smoking Related"	120	(58)	1.6	(1.0, 2.5)
Not "Smoking Related"	258	(55)	1.4	(1.0, 1.9)
Lip, Oral Cavity and Pharynx	17	(53)	1.3	(0.4, 3.8)
Digestive System	30	(60)	1.7	(0.8, 3.9)
Respiratory System	22	(50)	1.1	(0.5, 2.9)
Lung	13	(62)	1.8	(0.5, 6.6)
Bone, Skin and Connective Tissue	34	(32)	0.5	(0.2, 1.2)
Breast‡	51	(51)	1.1	(0.6, 2.1)
Female Genital Tract‡	113	(60)	1.6	(1.0, 2.6)
Cervix‡	70	(61)	1.7	(1.0, 3.0)
Prostate§	9	(44)	1.0	(0.2, 4.7)
Testis§	5	(80)	5.2	(0.5, 125.9)
Urinary Tract	5	(40)	0.8	(0.1, 5.7)
Eye, Brain and Other Nervous System	30	(63)	2.0	(0.9, 4.6)
Brain	24	(67)	2.3	(0.9, 6.0)
Endocrine Glands	20	(55)	1.4	(0.5, 3.8)
Hematopoietic Tissue	37	(68)	2.4	(1.1, 5.2)
Other	5	(80)	4.6	(0.5, 108.7)

*Missing values for father's smoking
†For comparison 47% of 438 controls were exposed to father's smoking
‡Sex specific comparison 48% of 288 female controls were exposed
§Sex specific comparison 43% of 150 male controls were exposed

Crude estimates of relative risk for cancers at specific sites in relation to father's smoking are shown in Table 3. The RR for "smoking related" (RR = 1.6) and for "not smoking related" sites (RR = 1.4) are similar. Specific sites with elevated RR included cervix, brain, and hematopoietic tissue.

[redacted] by spouse and mother are also taken into consideration.

Leukemia and lymphoma risk is also not substantially changed by adjustment for age, sex, race, spouse smoking, and individual smoking. The adjusted RR is 2.5. However, the risk is greater for individuals whose mothers also smoked (RR = 3.1 vs 1.8 for individuals whose mothers did not smoke) and the RR is 1.9 (95 per cent confidence limits = 0.9, 4.4) after adjusting for maternal smoking. For specific hematopoietic cancers, the crude RR was elevated for Hodgkins disease (RR = 5.7, 95 per cent confidence limits = 1.2, 38.4), non-Hodgkins lymphomas (RR = 1.6, 95 per cent confidence limits = 0.6, 4.3), and for acute leukemias (RR = 4.6, 95 per cent confidence limits = 0.6, 34.2).

Individual Smoking Status

Overall and site specific relative risk estimates are shown separately for individuals who smoked and those who never smoked in Table 4. Relative risk estimates in relation to mother's smoking are similar for smokers and nonsmokers and are close to one for all sites but hematopoietic tissue. Increased cancer risk related to father's smoking is not limited to smokers or nonsmokers, although the RR for all sites combined is greater among smokers.

Dose-response

The elevated risks for all cancers combined and for most specific sites were related primarily to father's smoking. However, for leukemia and lymphoma there is an increase in risk when both parents smoked. The RR is 1.7 when one parent smoked and 4.6 if both parents smoked (Mantel-Haenszel chi for trend = 3.25, $p < 0.001$). For both mother's and father's smoking, overall cancer risk increased only slightly with reported frequency of smoking in the house. Risk also tended to increase with reported number of cigarettes smoked, but a large proportion of missing values make these data unreliable.

Discussion

We have found overall cancer risk to be increased among the offspring of men who smoked. There was only a

TABLE 4—Cancer Risk from Parental Smoking among Nonsmokers and Smokers, All Sites Combined and Selected Sites†

Site	Maternal smoking						Paternal smoking					
	Nonsmokers			Smokers			Nonsmokers			Smokers		
	No	(% exposed)‡	RR	No	(% exposed)‡	RR	No	(% exposed)§	RR	No	(% exposed)§	RR
All Sites	191	(12)	1.2	227	(19)	1.0	173	(49)	1.2	205	(62)	1.7
"Smoking Related"	47	(9)	0.8	84	(15)	0.8	41	(56)	1.7	79	(59)	1.5
Not "Smoking Related"	144	(13)	1.3	143	(20)	1.1	132	(46)	1.1	126	(64)	1.8
Lip, Oral Cavity, and Pharynx	0	—	—	17	(12)	0.6	0	—	—	17	(53)	1.1
Digestive System	13	(8)	0.7	18	(11)	0.6	12	(50)	1.3	18	(67)	1.7
Respiratory System	4	(25)	2.9	18	(11)	0.6	4	(50)	1.3	18	(50)	1.0
Lung	1	(0)	0.0	14	(14)	0.7	1	(100)	∞	12	(58)	1.4
Bone, Skin, and Connective Tissue	19	(11)	1.0	17	(6)	0.3	20	(30)	0.6	14	(36)	0.6
Breast	29	(10)	0.9	24	(21)	0.9	28	(43)	0.9	23	(61)	1.4
Female Genital Tract‖	72	(11)	1.0	61	(25)	1.2	59	(51)	1.3	54	(70)	2.2
Cervix‖	40	(8)	0.7	40	(23)	1.3	34	(56)	1.7	36	(67)	2.0
Eye, Brain and Other Nervous System	17	(6)	0.5	20	(15)	0.8	15	(53)	1.5	15	(73)	2.8
Brain	11	(9)	0.9	20	(15)	0.8	9	(56)	1.7	15	(73)	2.8
Endocrine Glands	11	(18)	1.9	10	(20)	1.1	11	(55)	1.6	9	(56)	1.3
Hematopoietic Tissue	19	(21)	2.3	22	(41)	3.1	17	(65)	2.4	20	(70)	2.4

†Sites with 15 or more cases

‡For comparison: 11% of 220 nonsmoking controls and 18% of 235 smoking controls exposed to mother's smoking

§For comparison: 43% of 211 nonsmoking controls and 50% of 227 smoking controls exposed to father's smoking

‖Sex specific comparison: 45% of nonsmoking controls exposed to father's smoking and 11% exposed to mother's smoking; 52% of smoking controls exposed to father's smoking and 22% exposed to mother's smoking

small increase in risk associated with maternal smoking. Increased risk associated with father's smoking did not appear to be explained by differences in such factors as age, race, sex, social class (as measured by education and occupation), or smoking habits of the case or control. The effect was not limited to known smoking related sites. Estimated relative risks associated with father's smoking tended to be greater for smokers, males, and non-Whites. We have previously reported an increased cancer risk for individuals married to smokers,[29] but the apparent effect of paternal smoking is not altered by adjustment for smoking by spouse.

Several findings from different sources support the plausibility of increased cancer risk from early life exposure to cigarette smoke. In addition to the experimental studies[1-9] and biochemical studies in humans,[10-21] limited support for the results of the present study can be found in other epidemiologic studies.[22-24,27] Only one of these studies, however, has reported on cancer risk during adulthood from exposure to parent's cigarette smoke.[27]

Stewart, *et al*, in a large case-control study, found a very small (RR = 1.1) increased risk for cancer in children up to age 10 whose mothers smoked.[34] An increased cancer risk related to father's smoking was not seen (RR = 1.0), but 10 years may have been too soon to detect an effect. Neutel and Buck[22] found an increased risk (RR = 1.3) in a prospective study of cancer risk through age 10 among children whose mothers smoked during pregnancy, but did not report on father's smoking.

Questions on parental smoking during pregnancy have been included in a number of case-control studies of particular childhood tumors. Our finding of a two-fold increase in risk for brain cancer among individuals whose fathers smoked is consistent with the data of Preston-Martin, *et al*.[23] In their study, which focused on exposure to nitrosamines, an increased risk of brain cancer (RR = 1.5) among children whose fathers smoked during the mother's pregnancy was seen. Sidestream cigarette smoke which is passively inhaled is one source of exposure to nitrosamines and other N-nitroso compounds.[28] Gold, *et al*, did not report on father's smoking but found a five-fold increase in risk for brain tumors among children whose mothers continued to smoke in pregnancy.[35]

Findings from a study by Grufferman, *et al*,[24] are consistent with our finding of a predominantly paternal effect. In that study, an elevated relative risk for rhabdomyosarcoma was associated only with father's smoking. Manning and Carroll reported no increased risk for childhood leukemia related to mother's smoking.[25] Father's smoking was not reported. Although the number of cases was small and dose-response data were inconsistent, Neutel and Buck did find that the offspring of smoking women had nearly twice the leukemia risk of offspring of women who did not smoke.[22]

Despite the small number of lung cancer cases included, we chose to look at lung cancer risk in relation to paternal smoking because of continued interest in passive smoking and cancer risk at this site.[27,36,37] The RR for lung cancer among individuals whose fathers smoked was 2.5 after adjusting for age and individual smoking. The adjusted RR associated with mother's smoking was 1.8, but this was based on only two smoking mothers among 15 cases. Correa, *et al*, reported an RR of 1.7 for lung cancer associated with mother's smoking, but no increased risk related to father's smoking.[27]

Our finding of a possible cervical cancer risk related to father's smoking has not been reported elsewhere. There is, however, growing support for a role of passive smoking (as measured by spouse smoking) in cervical cancer risk.[38,39]

Data on parental smoking were obtained retrospectively from offspring who may not be in a position to provide accurate histories. Parents or siblings of study subjects were

also interviewed regarding the smoking histories of the parents to validate the data obtained from subjects. We interviewed 649 relatives of subjects included in this report. Of these, 55 per cent were mothers and 40 per cent were siblings. For more than 350 subject-mother pairs, agreement on qualitative smoking questions ranged from 93 to 98 per cent and was substantially better than chance. There was also good agreement between subjects and their siblings.

Our findings are not due to any obvious recall bias. The hypothesis that parental smoking may cause cancer is not generally well known and study subjects and interviewers were told only that we were interested in smoking patterns in families. We obtained similar responses from mothers and subjects, regardless of case status, suggesting that differential recall probably did not occur.

It is difficult to distinguish transplacental and passive childhood exposures in an epidemiologic study: women who smoke during pregnancy generally continue smoking after the baby is born.[40] Father's smoking may produce transplacental as well as passive childhood exposure.[13,16,20] An effect of father's smoking on genetic material in sperm is also a possibility.[41-43] Only 16 per cent of the smoking mothers in our study began smoking after pregnancy, and no mothers smoked only during pregnancy. This made it difficult to compare cancer risks for individuals exposed in utero with risk in individuals exposed only passively in childhood. Furthermore, 94 per cent of the smoking fathers smoked both before and after the subject's birth.

Nevertheless, if an increased risk were seen for mother's but not father's smoking, a transplacental effect might be a reasonable explanation. In this study and others,[23,24] increased risks were generally related to father's smoking only. Little increased risk was associated with mother's smoking, suggesting a passive rather than a transplacental mechanism. Our failure to find a similar effect for mother's smoking might be due to the fact that they smoked fewer cigarettes than fathers or smoked different types of cigarettes. Although children may spend more time with their mothers than with their fathers, it is also conceivable that mothers do not smoke when actively engaged in child care activities.

The increasing frequency of women smoking after the 1920s should provide future studies with increasing power to detect any late effects of maternal smoking on offspring. The first sizable cohort of individuals exposed to maternal smoking is only beginning to reach the age at which cancer most commonly occurs.

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Mortality Rates in Boston (and Other Large Cities), 1911

Boston's death rate for 1911 was 17.1, which is high compared with rates of most other large American cities.

The 1911 rates for the other cities having over 500,000 inhabitants were—Cleveland 13.55; Pittsburgh 14.94; Chicago 14.55; New York 15.22; St. Louis 15.36; Philadelphia 16.51; and Baltimore 18.43.

A brief analysis of these rates is desirable.

Typhoid Fever:—*From typhoid Boston had the lowest rate of all the cities. The rates per 100,000 were as follows:—Boston 9.14; Chicago 10.78; New York 10.99; Philadelphia 14.11; Cleveland 14.46; St. Louis 15.56; Pittsburgh 25.81; and Baltimore 27.28.*

Scarlet Fever:—*The rates were Baltimore 7.79; Pittsburgh 9.95; Boston 10.74; Philadelphia 11.33; New York 13.25; Chicago 21.20; St. Louis 27.26; and Cleveland 31.12.*

Diphtheria:—*The rates were Baltimore 12.05; St. Louis 16.84; Boston 18.00; Cleveland 21.94; Pittsburgh 23.60; New York 25.84; Philadelphia 31.51; and Chicago 39.11.*

Measles:—*The rates were Chicago 5.75; Cleveland 6.63; Pittsburgh 9.59; Boston 10.74; New York 13.25; Baltimore 13.63; St. Louis 15.84; and Philadelphia 19.30.*

Whooping Cough:—*The rates were Chicago 2.45; St. Louis 4.57; Philadelphia 7.34; New York 7.75; Baltimore 8.50; Cleveland 14.80; Boston 15.68; and Pittsburgh 19.54.*

Taking all these diseases together, Boston had the lowest rate with 64.30 per 100,000; the others in order were Baltimore 69.25; New York 70.88; Chicago 7.29; St. Louis 80.07; Philadelphia 83.59; Pittsburgh 88.49; and Cleveland 88.95.

Tuberculosis of the Lungs:—*The rates per 100,000 were Cleveland 121.77; Pittsburgh 130.88; St. Louis 135.29; Boston 154.88; Chicago 165.98; New York 177.39; Philadelphia 187.31; and Baltimore 205.12.*

This analysis of the communicable diseases should be extremely gratifying to the people of Boston. However, it fails to reveal the reason of Boston's higher rate. But a study of the figures for 1910, for which year more complete figures are available, will show much more. . . .

Cancer, cerebral hemorrhage, organic diseases of the heart, pneumonia and violent deaths stand out as the principal causes which have comparatively high rates in Boston. . . .

There are two reasons why Boston has such a large number of deaths of non-residents. First it has a population in its immediate suburbs greater than the population of the city itself. These people labor in Boston and when ill come to Boston hospitals. The other reason is that Boston is the recognized medical centre for all New England and attracts those afflicted with cancer, for example, a disease more prevalent in the New England States than in any of the other registration states.

Moreover in 1910 Boston had a larger percentage of its deaths over 6 years of age than any of the cities under consideration. In a word, Boston is an old city and has many old people. . . .

But in a word it may be safely said that Boston's high rate is largely due to its geographical position in the centre of populous suburbs, and to its fame as a medical centre, and not, as has been so often intimated, to the unhealthful conditions in the city.

—Davis WH: Boston's death rate. Am J Public Health 1912; 2:638–640.

Preliminary Communication

CUMULATIVE EFFECTS OF LIFETIME PASSIVE SMOKING ON CANCER RISK*

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Summary Cancer risk from cumulative household exposure to cigarette smoke was evaluated in a case-control study. Overall cancer risk rose steadily and significantly with each additional household member who smoked over an individual's lifetime. Cancer risk was also greater for individuals with exposures during both childhood and adulthood than for individuals with exposures during only one period. These trends were observed for both smoking-related and other sites. These findings are preliminary and must be confirmed with other studies. Nonetheless, they suggest that effects of exposure to the cigarette smoking of others may be greater than has been previously suspected.

INTRODUCTION

INCREASED risk of respiratory illness in children,[1-3] changes in respiratory function in children and adults,[4,5] risk of childhood tumours,[6-8] and risk of lung cancer and possibly other adult cancers[9-14] have all been reported as possible effects of exposure to other people's cigarette smoke (passive smoking). Adult cancer risk from childhood exposure to parents' smoking has also been discussed.[14,15] These studies considered the independent effects of exposure in one period to cigarette smoke from only one source, even though individuals may be exposed to a number of sources over their lifetime.

*Some of this material was presented at the annual meeting of the society for Epidemiologic Research, June, 1984, Houston, Texas USA.

In a study of adult cancer risk related to parents' smoking[15] we collected data on exposure to cigarette smoke of not only parents, but also spouses and other household members. In the present study cancer risk in relation to cumulative passive exposure to cigarette smoke was examined. We did not collect data on exposures outside the home, but were able to consider whether cancer risk increases with the number of household members who smoke.

METHODS

Study methods have been reported elsewhere.[13,15] Cancer patients were selected from a hospital-based tumour registry. They included all those with cancer diagnosed between July 1, 1979, and March 31, 1981, and assumed to be alive on March 31, 1981. Patients ranged from 15 to 59 years of age at the time of diagnosis, and all cancer sites except basal-cell cancer of the skin were included. Patients were restricted to age 59 and younger to maximise the likelihood of maternal smoking, since few women were smokers before 1920.

Of 740 eligible cancer patients identified from the tumour registry, 107 (14%) died before we could contact them. An additional 115 (16%) either refused to participate or could not be contacted. 518 (70%) patients completed questionnaires. Control subjects were cancer-free and of the same race, sex, and age (±5 years) as patients. They were friends or acquaintances of patients (n = 309) or were randomly selected by systematic telephone sampling (n = 209). Patients and control subjects were also similar in occupational category and smoking habits. Analysis was restricted to individuals who lived with both natural parents for most of the first 10 years of life. Results are reported for 369 patients and 409 control subjects who supplied information about the smoking habits of their spouse and parents.

Information on exposure to cigarette smoke was obtained by means of a structured questionnaire that was sent to all subjects. Another questionnaire was sent and follow-up telephone calls were made when a response to the first questionnaire was not obtained. Childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents and information on other household members who smoked. Subjects were considered to be exposed during childhood if one or both parents smoked cigarettes in the house before the subject was 10 years old or if one or more other household members smoked during that period. Passive exposure to cigarette smoke during adulthood was estimated from the number of years of marriage during which a spouse smoked. Subjects were considered to be exposed if they had a spouse who smoked regularly at any time during their marriage. Active smokers were defined as those who ever smoked as many as 1 cigarette a day for as long as 6 months.

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TABLE I—OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE

—	Number of household members who smoke			
	0	1	2	3 or more
Combined group				
Patients	54	127	123	48
Control subjects	99	161	97	34
Odds ratio	1·0	1·4	2·3*	2·6*†
Active smokers‡				
Patients	22	60	78	35
Control subjects	38	73	60	25
Odds ratio	1·0	1·4	2·2*	2·4*†
Non-smokers				
Patients	32	67	45	13
Control subjects	61	88	37	9
Odds ratio	1·0	1·5	2·3*	2·8*†

*Statistically significant differences between risk with specified number of exposures and with no exposure, $p<0·05$.
†Statistically significant χ^2 for trend, $p<0·01$.
‡Current smokers and ex-smokers.

We have found[13,15] that exposure to parents' or spouse's smoking contributed independently to cancer risk—ie, adjusting for one exposure did not alter the risk associated with the other. Thus we used two approaches to measure the effects of multiple exposures: cancer risk was examined in relation to the total number of household members who smoked, irrespective of when the exposures occurred, and in relation to the period during which the exposures occurred (childhood or adulthood only, or both periods). Odds ratios were calculated and a chi-square test was used to assess statistical significance. A chi-square test for linear trend was used to evaluate the risk with increasing numbers of exposures in unadjusted[16] and adjusted[17] analyses.

RESULTS

Cancer risk associated with exposure to increasing numbers of household members who smoke is shown in table I. A smoking mother, father, spouse, or 1 or more additional household members who smoked during the patient's childhood or a spouse who smoked while married to a patient each counted as one exposure. The total number of exposures is the sum of the individual exposures. Overall cancer risk increased significantly with increasing numbers of exposures, with odds ratios rising from 1·4 for 1 exposure to 2·3 for 2 exposures and 2·6 for 3 or more exposures. Statistically significant linear trends were also seen when smokers and non-smokers were considered separately. Adjustment for potential differences in age, race, sex, and educational level did not alter these trends.

TABLE II—OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE IN CHILDHOOD AND ADULTHOOD

—	Age period of exposure			
	No exposure	Childhood only*	Adulthood only†	Both
Patients	54	107	58	145
Control subjects	99	124	72	98
Odds ratio	1·0	1·6‡	1·5	2·7‡§
		1·5‡ (childhood or adulthood only)		

*Exposure to smoking mother, father, or other household member during childhood.
†Exposure to smoking spouse.
‡Statistically significant differences between risk with specified exposure and no exposure, $p<0·05$.
§Statistically significant linear trend: no exposure, exposure in only one time period, exposure in both time periods, χ^2 for trend = 23·7, $p<0·01$.

We also measured cancer risk in relation to the period when exposures occurred (table II). Risk rose by 60% for individuals exposed during childhood only and by 50% for individuals exposed during adulthood only but was more than doubled for those exposed during childhood and adulthood (odds ratio = 2·7). There was a significant linear trend in risk for individuals exposed in no, 1, or 2 periods. Again trends were similar for smokers and non-smokers and were not affected by adjustment for potential confounding factors.

TABLE III—CANCER RISK FROM MULTIPLE HOUSEHOLD EXPOSURES TO CIGARETTE SMOKE: SITES WITH 15 OR MORE CASES*

Site	Number of cases	Number of exposures			
		0	1	2	3 or more
All sites	369	1·0	1·4	2·3	2·6‡
Smoking related†	115	1·0	1·8	3·0	3·8‡
Other	254	1·0	1·5	2·4	2·6‡
Buccal cavity and pharynx	15	1·0	4·9	5·1	2·9
Digestive tract	30	1·0	0·7	1·8	1·3
Respiratory tract	19	1·0	0·7	0·6	2·9
Breast	48	1·0	2·0	2·4	3·3‡
Cervix	62	1·0	1·6	3·6	3·4‡
Eye, brain, and other nervous system	29	1·0	2·3	2·3	0·7
Thyroid	19	1·0	1·0	3·1	8·7
Leukemia and lymphoma	37	1·0	2·5	5·1	6·8‡

*Odds ratios are given.
†Includes oral cavity and pharynx, oesophagus, pancreas, respiratory tract, urinary tract, and cervix.
‡Statistically significant linear trend.

Cancer risk increased with increasing numbers of household exposures to cigarette smoke for smoking-related sites and for other sites that are not thought to be smoking related (table III). Smoking-related sites included cancers of the oral cavity and pharynx, oesophagus, pancreas, respiratory tract, urinary tract, and cervix. For smoking-related sites odds ratios for 1, 2, and 3 or more exposures were 1·8, 3·0, and 3·8, respectively. The trend for the other sites combined was also statistically significant but the risk was less than that for smoking-related sites. The trends for cancers of the breast and cervix and for leukaemia and lymphoma combined were significant, but the trend for cancer of the respiratory tract was not.

DISCUSSION

If passive smoking has an effect on cancer risk the nature and extent of that risk are likely to differ for childhood and adult exposures. The clear overall trends found in this study might be associated with carcinogens present in tobacco smoke acting through multiple mechanisms at different periods of life. We found the risk of all cancers increased steadily and significantly with cumulative lifetime exposure to household members who smoke. This trend was not altered when adjustment was made for confounding variables.

Our findings must be regarded as preliminary. Prompted in part by experimental evidence[19] we initially intended to measure the effect of transplacental or early childhood exposure to carcinogens on cancer risk in adulthood. We chose to investigate cigarette smoke because exposure to this carcinogen is both common and measurable. The finding of a cumulative lifetime risk from passive smoking was unexpected.

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We collected information on most possible sources of cigarette-smoke exposure that would be encountered during childhood but the only adult exposure we considered was that resulting from the smoking of a spouse. We did not validate information on smoking habits of spouses but interviewed more than 700 relatives of patients and control subjects to validate the quality of parental smoking histories provided by adult offspring. Study subjects provided adequate information on parents' smoking, and the quality of these data did not differ between patients and control subjects.

For adults in the United States exposures to cigarette smoke outside the home may be important.[20] Also the frequency of exposure to other people's cigarette smoke may change with age, with the peak exposure possibly occurring during a person's 20s.[20] We did not take exposures outside the home or age-related changes in exposure frequency into account.

Our data are limited by small numbers of any specific cancer site, by certain characteristics of our study sample, and by other features of our method.[13,15] No conclusions about the impact of passive smoking relative to the effects of direct smoking can be made, since the selection of friends as control subjects meant they were usually matched with patients on smoking status. We confirmed the quality of our data and ruled out many, but not all, potential confounding factors.

Although the passive smoker receives a quantitatively lower exposure than the active smoker, that exposure is qualitatively richer in many smoke constituents: there is 3 times as much benzo(*a*)pyrene, 6 times as much toluene, and more than 50 times as much dimethylnitrosamine in a fixed volume of sidestream smoke in the gas phase as there is in cigarette smoke inhaled by the active smoker.[18] The potential for damage from passive exposure may be greater than has been previously recognised.

Our finding of dose-dependent cancer risks for sites not considered to be related to active smoking might be questioned because active smokers are also passively exposed. For some sites it is not clear in the literature if no risk from direct smoking exists or if a possible link has not yet been investigated. For other sites, such as the breast, some studies have found no cancer risk associated with smoking.[21] One possible explanation for this discrepancy is that in studies comparing smokers with non-smokers, passive smokers are included in the non-smoking group. This would make it difficult to detect a small difference in risk due to smoking. Few studies have evaluated the effects of passive smoking on risk of cancer at sites other than the lung. Furthermore, there is little data available on the effects of transplacental or childhood exposure to cigarette smoke on cancer risk in adulthood.

Data from biochemical and experimental studies support our findings though many of these reports must be regarded with caution. There is evidence that non-smokers are exposed to potential carcinogens through the cigarette smoking of others. Cigarette-smoke by-products such as cotinine and thiocyanate have been measured in the blood, urine, and saliva of non-smoking adults, children, and fetuses exposed to smokers,[22-26] and there has been at least one report of raised levels of mutagens in urine of passive smokers.[27] Greater activity of enzymes that metabolise benzo(*a*)pyrene has been noted in placentas of smokers[28-30] and even passive smokers.[31] Similar increases may occur in tissues of fetuses, children, or adults exposed to smokers.

Studies in laboratory animals provide evidence in support of an adult cancer risk from transplacental or childhood exposure to cigarette smoke, but this hypothesis has not been tested directly.[19] Data from these studies show that many carcinogens, including those in cigarette smoke, are active when administered transplacentally or during early life and may produce effects at lower doses than those required for adults.[32-36] Some low-dose exposures which are not in themselves carcinogenic increase the sensitivity of exposed animals to later carcinogenic exposures.[37,38] In other experiments tumours resulting from transplacental and early postnatal exposures were not apparent until the animals were fully developed and did not necessarily differ in site or morphology from spontaneously occurring tumours.[32,39] This is consistent with our finding of raised risk for adult tumours at many sites.

Future studies should include cancer sites not necessarily associated with active smoking and should take into account childhood sources of passive smoke exposure.

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References continued at foot of next page

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It is unclear whether the result in the youngest cohort can be explained by aggressive tumour growth, by too low a sensitivity of the mammographic test, by too short a follow-up, or by chance. The absence of any effect so far in the youngest age-group corresponds with the early results of the age-group 40–49 at entry in the Health Insurance Plan (HIP) trial. 5 years after the HIP screening programme had begun, the number of breast cancer deaths was 19 in the study group and 20 in the control group (RR = 0·95).[3] 10 years after the start the RR was 42/54 (0·78), and 14 years after the start it was 46/61 (0·75).[4] Nevertheless the HIP investigators hesitated to accept this finding as evidence of the effectiveness of screening under age 50.

In Nijmegen a disease stage classification system according to mammographical and/or histopathological tumour size was used. "Advanced stage" means that the axillary lymph nodes were histologically involved or that the lesion consisted of infiltrative carcinoma and was at least 2 cm in size. In the age-group 35–49 at diagnosis 38% of 40 screen-detected cases had advanced disease stage, as opposed to 4 out of the 6 cases in women who did not participate in the screening programme. According to these figures a subsequent mortality reduction can be expected in the youngest age-group.

Finally, attention should be paid to the weak effect of screening on breast cancer mortality in the oldest age-group. It is assumed that breast cancer grows rather slowly in this group.[5,6] As a consequence, the lead-time should be very long, and a strong effect could be expected after a longer period of follow-up. The odds ratio for the birth cohort born before 1910 is now only 0·81. Maybe this RR estimate is weak because of different underlying mortality risks (independent of any screening effect) in the participating and non-participating groups. Maybe differences in patient's delay explain that the effect was less favourable than expected. And maybe selective misclassification of the death certificates is another explanation. Further studies will focus on these potential biases.

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LIFETIME PASSIVE SMOKING AND CANCER RISK

SIR,—Dr Sandler and colleagues (Feb 8, p 312), in a preliminary report, describe the relative cancer risk for persons living in households with 0, 1, 2, and 3 or more members who smoke. The risk increased, both for active and for non-smokers, with the number of household members who smoked, and Sandler et al suggest that exposure to ambient smoke in the household might be responsible.

In table I they normalise the odds ratio for cancer risk to unity for households with no (other) smokers and disregard exposure to cigarette smoke outside the home. Calculating to two decimal places, the odds ratios for households with 1 (other) smoking member are 1·42 for active smokers and 1·45 for non-smokers; for households with 2 (other) smokers the corresponding ratios are 2·25 and 2·32; and for 3 or more, the ratios are 2·42 and 2·75. The risk ratios for active smokers are therefore, within the error limits, the same as for non-smokers; to simplify the argument, I shall treat them as identical.

Suppose the average risk of cancer is N from all causes unconnected with smoking, A from active smoking, and P from passive smoking. An active smoker is also a passive smoker of his own ambient cigarette smoke, so the total cancer risk for active smokers in households with no other smoker is $N+A+P$; in households with 1 other smoker the risk is $N+A+2P$. For non-smokers, the corresponding risks are N and $N+P$. Because the data of Sandler et al imply that odds ratios (and hence the ratios of relative risks) are virtually identical we require that $(N+A+2P)/(N+A+P)=(N+P)/N$. In other words $A+P=0$. This same relation is obtained from relative risks in households with 2 and with 3 or more (other) smokers. A multiplicative model, in which the cancer risk in, for example, an active smoker in a household with no other smokers is of the general form, $N(1+A+P)$, where A and P are now proportional to the concentration of effective carcinogens in active and passive smokers, respectively, also yields the same equality.

The relation $A+P=0$ leaves us with three possible interpretations:

(1) Active and passive smoking are both non-carcinogenic ($A=P=0$). (2) Active smoking is carcinogenic and passive smoking is prophylactic ($A=-P$). (3) Active smoking is prophylactic and passive smoking is carcinogenic ($P=-A$).

The statistical uncertainty in Sandler's table I is large enough to permit slightly less paradoxical inferences, but let us pursue the unthinkable a little further.

Three randomised controlled intervention trials (the Oslo study,[1] the Whitehall study[2] and MRFIT[3]) provide a direct epidemiological test of the hypothesis that giving up active smoking reduces the risk of cancer. In the "intervention" (low-smoking) groups in these three trials together there were (including registrations as well as deaths in the Whitehall study[2]) 149 cancers in a combined entry population of 7746 (1·92%); while in the relatively high-smoking control groups there were 121 cancers in 7797 (1·55%). From the orthodox viewpoint—namely, active smoking causes at least 30% of all cancers—these findings are as paradoxical as the inferences from Sandler's study. We might just be able to postulate complicated, though implausible, causal models to account for Sandler and colleagues' table I, or we may put those results on one side because of their preliminary character. It is more difficult to evade the implication of the methodologically reputable randomised trials: active cigarette smoking has little or no net carcinogenic action.

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SIR,—Dr Sandler and colleagues' paper on the cumulative effects of lifetime passive smoking on cancer risk appears seriously flawed. They compared 518 out of a total of 740 cancer patients aged 15–59 from a hospital-based tumour registry, with 518 controls of the same age, sex, and race. 309 controls were friends or acquaintances of the patients and 209 were randomly selected by systematic telephone sampling. Results are presented for 369 (70%) cases and 409 (79%) controls. Apart from death before the subjects could be contacted and refusal, only those persons who had "lived with both natural parents for most of the first ten years of life" were analysed. We are told that they supplied information about the smoking habits of their spouse and parents. Presumably, they also supplied information about their own smoking.

The results are shown in three tables, only one of which differentiates between active and passive smoking, and none of which differentiates between sex, age, and race. The belief that these factors do not matter because they were matched for is unsound. The reader has no idea how differences between those

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initially chosen and those finally analysed could have influenced the results. Moreover, as soon as the groups are stratified by active smokers and never smokers, the matching is broken. Until the results have been presented for non-smokers by age, sex, and race no conclusions can be drawn.

Furthermore the truncated age group (15–59 years) has resulted in an unrepresentative selection of cancer cases. Even so, the distribution by cancer site seems strange: there were 62 (17%) cancers of the cervix uteri but only 19 (5%) cancers of the respiratory tract and 48 (13%) breast cancers. The trend in cancer risk from multiple household exposures to cigarette smoke is least impressive for cancer of the respiratory system, where an effect might be expected to be greatest, and most striking for leukaemia and lymphoma where any biological explanation is, to say the least, obscure. The most extraordinary finding appears to have been the very similar trends in cancer risk with number of household members who smoke irrespective of whether the cases smoked or not. Indeed, Sandler and colleagues' publication on the same material in the *American Journal of Epidemiology* (1985; **121:** 37–48) shows that the effect of passive smoking on cancer risk appears to have been greater than the effect of active smoking.

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, These letters have been shown to Dr Sandler and colleagues, whose reply follows.—ED. L.

SIR,—Professor Burch presents an algebraic rearrangement of our data that suggests that smoking is protective. His approach assumes that childhood and adulthood exposures are interchangeable. As we indicated in our paper, the apparently linear trends in table I simplify a complex set of relationships. Our data illustrate that childhood and adulthood exposures may contribute independently to cancer risk in adulthood, but this does not imply that these two exposures are equivalent. Data we present elsewhere suggest the two risks may, in fact, be different (ref 1, and unpublished). As shown in the accompanying expansion of table II, the odds ratio associated with passive exposure only as an adult was 1·8 for non-smokers but only 1·2 for active smokers (not equal, as Burch's analysis requires). For childhood exposures, the opposite was true: the odds ratio was 1·9 for smokers and 1·3 for non-smokers. Thus, passive exposure in childhood seems to have its greatest effect among persons later exposed to a carcinogen (their own smoking), while passive exposure in adulthood has its largest effect among persons not actively exposed. In short, our data do not support the simplified biological assumptions Burch requires for his analysis.

Dr Higgins raises concern about possible biases in the study and requests additional data. The information he seeks is provided in a paper he cites.[1] As explicitly stated in both papers, there was no confounding by the variables mentioned by Higgins. The "truncated" age group was chosen because a primary aim of our study was to evaluate effects of mothers' smoking. Since few women smoked before 1920, we studied cases who were younger than age 60 in 1980. It will be several years before cancer risk associated with mothers' smoking can be evaluated for older persons. The distribution of cancer sites studied resulted from methodologic decisions and hospital referral patterns which were discussed in the papers. Nonetheless this group was not preselected on the basis of any prior hypothesis, and it is not easy to see how inclusion of more cancers that are "unrelated" to cigarette smoking would lead to an inflated overall cancer risk from passive smoking.

OVERALL CANCER RISK FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE IN CHILDHOOD AND ADULTHOOD

	No exposure	Age period of exposure: Childhood only*	Age period of exposure: Adulthood only†	Both
Active smokers				
Patients	22	63	25	92
Controls	38	58	37	65
Odds ratio	1·0	1·9¶	1·2	2·4‡,§
		1·6 (childhood or adulthood only)		
Non-smokers				
Patients	32	44	33	53
Controls	61	66	35	33
Odds ratio	1·0	1·3	1·8‡	3·1‡,§
		1·5 (childhood or adulthood only)		

*Exposure to smoking mother, father, or other household member during childhood.
†Exposure to smoking spouse.
‡Significant differences between risk with specified exposure and no exposure ($p<0·05$).
¶$p=0·051$.
§Statistically significant linear trend: no exposure, exposure in only one time period, exposure in both time periods (χ^2 for trend, $p<0·01$).

Higgins cites our finding of a leukaemia effect as one for which "any biological explanation is, to say the least, obscure". On the contrary, cigarette smoke contains chemicals known to be leukaemogenic, and has been associated with increased leukaemia risk in many,[2–5] although not all[6] studies. Some of these studies find an apparent dose-response, especially for non-lymphocytic leukaemias.[2,3,5] The 40–50% increase in leukaemia risk among smokers is much smaller than that reported for other sites such as the lung, which may account for the lack of interest in smoking and leukaemia. Experimental and biochemical data from a variety of sources (refs 7 and 8, and discussed in our papers) are also consistent with a possible association between leukaemia risk and exposure to cigarette smoke.

There is one final point. Our study was not designed to compare the effects of active and passive smoking. Our method of choosing friend controls inadvertently matched for active smoking, which erases the possibility of observing an effect due to active smoking. Higgins' comparison of the effects of active and passive smoking is not meaningful in our data.

The questions raised by Burch and Higgins do not persuade us that our study is "seriously flawed". We stress the need for additional studies and strongly urge investigators to consider that the range of possible effects from active and passive exposure to cigarette smoke may be broader than has been thought.

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REDUCED RESPONSE OF URAEMIC BLEEDING TIME TO REPEATED DOSES OF DESMOPRESSIN

SIR,—Treatment with desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) shortens prolonged bleeding times in patients with von Willebrand disease,[1] platelet defects,[2] and uraemia,[3-5] and in healthy subjects.[2] The bleeding time correction by desmopressin has been attributed to the raising of plasma concentrations of high-molecular-weight forms of factor VIII (FVIII) related antigen and von Willebrand factor (vWF) activity.[6] In uraemia FVIII-vWF concentrations are normal to high even before desmopressin; here, the presence of abnormal multimers may explain why normal multimers, provided via desmopressin[5] or cryoprecipitate[5-7] are effective.

Published experience with desmopressin in uraemia is limited to short-term responses. When we gave cryoprecipitate (30 ml/kg) in

of urease; all these specimens yielded a heavy growth of *C pyloridis*. One-third of tests were positive by 3 h and half by 6 h.

The advantage of this rapid test is the achievement of a diagnosis of *C pyloridis* gastritis on the same day that patients attend for endoscopy, thus avoiding a second hospital appointment. We have found this very useful for the enrolment of patients into a therapeutic trial comparing medications.

We thank our colleagues for obtaining the biopsy samples.

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CAMPYLOBACTER PYLORIDIS IN PEPTIC ULCER

SIR,—We read with interest Dr Rathbone and colleagues' letter (May 25, p 1217) in response to our April 20 report and apologise for our failure to make it clear that all peptic ulcer patients were diagnosed by endoscopy and that the sera studied were collected before treatment. The antibody assays were performed under code.

The 50 members of laboratory staff did not undergo endoscopy (for obvious reasons) nor have they been labelled as a reference group. Similar remarks apply to the children's sera, which were a general collection referred to our hospital for viral studies. The purpose of our communication was solely to report the difference found between these cohorts. The data encourage speculation as to a link between *Campylobacter pyloridis* and peptic ulcer. The raised titres in well people may be due to symptomless infection, perhaps a carrier state—this is not unknown in infectious diseases and has provided a stimulus to epidemiologically based studies.

Rathbone et al suggest that under some circumstances a specific gut IgM response might occur without either an IgA or IgG response. This is at odds with generally accepted mechanisms of gut immunity, which regard IgA as the first immunoglobulin of response in the gut.[1]

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LIFETIME PASSIVE SMOKING AND CANCER RISK

SIR,—Dr Sandler and colleagues (Feb 8, p 312) present results in their table I showing that odds ratios for overall cancer risk increase markedly in relation to the number of household members who smoke, and this increase is similar for active smokers as for non-smokers. Professor Burch (April 13, p 866) comments that this similarity leads to the paradoxical conclusion that the average effects of active smoking and passive smoking must be equal and opposite. In reply, Sandler and colleagues point out that this equality is in reality a superficial averaging of two findings—a greater odds ratio for non-smokers than smokers in relation to passive smoking as an adult, and a greater odds ratio for smokers than non-smokers in relation to passive smoke exposure in childhood. Surely, however, the latter finding is even more implausible than equality of effect in smokers and non-smokers. On any plausible model, the relative effect of passive smoking should be greater in non-smokers, who start from a smaller background level, than in smokers. Mathematically, if β is the background level of risk in the absence of passive smoke exposure and δ the increment in risk resulting from passive smoke exposure, the odds ratio $(\beta+\delta)/\beta$ will tend to be smaller the greater the value of β.

Sandler's findings are implausible in other respects—notably the large effect claimed for passive smoking for a number of cancers (breast, thyroid, leukaemia/lymphoma) that are generally believed to have little or no relationship to active smoking—and attention must inevitably centre on the adequacy of the study methods used. The choice of controls used in this study, a mixture of friends or acquaintances of patients and people randomly selected by systematic telephone sampling, is certainly unusual and seems very open to question. Sandler and colleagues admit that the study cannot be used to relate active smoking to risk of cancer, since estimates will be biased by the similarity of active smoking habits of friends. Surely, since active and passive smoking are strongly correlated, bias in studying the relationship of passive smoking to risk of cancer will also arise.

Bias may also arise because of the difference in method of approach. Thus, in a separate paper,[1] Sandler et al note that the proportion of subjects not answering questions on marital status was over three times greater in controls than in cases. If there are highly significant differences in the proportion of certain questions being answered at all, how does one know that there are not highly significant differences in the way the passive smoking questions are dealt with?

Given that active smokers receive substantial passive smoke exposure from their own cigarettes, it is a priori implausible that passive smoking should increase risk of cancers that are not associated with active smoking. Seen in this light, a much more appropriate analysis of Sandler's data would be to treat patients with smoking-related cancers as cases and patients with non-smoking-related cancers as controls. Calculations from data presented in table III of their *Lancet* paper indicate that there is no significant relation between passive smoking and cancer risk if the data are analysed in this way. This is a more plausible finding, and consistent with the results of my 1984 review[2] which concluded that there is as yet no convincing evidence that passive smoking results in any material risk of serious health hazards.

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SIR,—In their reply accompanying my letter of April 13 (p 866) Dr Sandler and colleagues misrepresent me as arguing that "smoking is protective". In fact I pointed to three possible interpretations of their findings and concluded that "active smoking has little or no net carcinogenic action". The new breakdown of their findings does not eliminate the paradoxes implicit in the aggregate data.

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BENZTROPINE INHIBITS TOXICITY OF MPTP IN MICE

SIR,—The discovery that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes irreversible parkinsonism in man and other primates has provided new clues as to the cause of Parkinson's disease. The ability of MPTP to produce a relatively specific destruction of dopaminergic nigrostriatal neurons can be prevented by inhibitors of the enzyme monoamine oxidase B, including deprenyl, in primates[1,2] and mice.[3] Deprenyl (selegiline hydrochloride) has been in use in Europe for some years as an adjunct to levodopa treatment because of its ability to inhibit dopamine catabolism in the brain. Now it is suggested that early treatment with deprenyl might slow or even prevent progression of Parkinson's disease by preventing toxicity of some MPTP-like substance conceived as responsible for Parkinson's disease.

MPTP is not neurotoxic; its oxidation product MPP^+ (1-methyl-4-phenylpyridine) is.[4] MPP^+ accumulates in nigrostriatal neurons via the dopamine neuronal uptake system; MPP^+ uptake into rat striatal synaptosomes is inhibited by dopamine uptake inhibitors

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Letters to the Editor

RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is unfortunate that Sandler et al. (1) did not obtain information on, or account for, additional possible confounding variables in their study. The only ones that they report having included were age, sex, race, active smoking, education, blue collar vs. white collar occupation, and parental smoking. We have found that the amount of passive smoking was correlated with self-reported exposure to occupational hazards, use of marijuana, and alcohol intake (2). Thus, for example, the increased risk of breast cancer observed by Sandler et al. may be due to increased alcohol intake (3) rather than to passive smoking. Perhaps exposure to occupational hazards explains the slightly increased risk of hematopoietic cancer (4) among passive smokers, and husbands' sexual behavior associated with the smoking habit (5) accounts for an increased risk of cervical cancer. The authors alluded to this last possibility, but did not rule it out.

Sandler et al. (1) were careful to point out that the associations that they found "... might relate to other factors we have not measured or to deficiencies in study design." However, they went on to state that they "have not been able to identify a possible confounder ... that could have caused the difference in smoking patterns of spouses between cases and controls." The above suggestions represent a few possibilities.

Sandler et al. also pointed out that sidestream smoke has higher concentrations of certain carcinogens than mainstream smoke. Nevertheless, because (a) the dosage of smoke is so much lower in passive than in active smoking, and (b) smokers also "passively" breathe sidestream smoke in addition to inhaling mainstream smoke, it would be surprising if passive smoking actually caused any cancers that were not associated with active smoking.

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RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

Sandler et al. (1) removed much of the impropriety of their demonstration of an effect of passive smoking generally in raising the risk of cancer by focusing particular attention on the instances in which the study case was a nonsmoker. But substantial impropriety remains.

First, it gives cause to wonder how passive smoking could give rise to a doubled rate of cancer generally, including cancer of sites not previously associated with direct smoking of cigarettes. Those specific sites are only identified in their table giving results for nonsmokers plus smokers combined, with the added risk for passive smoking then shown at 60 per cent. The crude added risk of lung cancer from passive smoking, smokers plus nonsmokers combined, is shown as 90 per cent, but based on only 22 cases of lung cancer—of whom only two were nonsmokers. So only two nonsmoking lung cancer cases were available for judging the true effects of passive smoking on lung cancer.

Elsewhere (2), the study of passive smoking has focused specifically on lung cancer and specifically among individuals who themselves were nonsmokers, i.e., the nonsmoking wives of smokers, and, even so, such studies have been subject to criticism (3).

In Sandler et al. (1), the authors have given ostensible concern for potential confounding factors. Perhaps others would agree that confounding factors have been taken into account, but not in my opinion. The issue of what is a confounding factor has become so confused that I have hesitated to get into the fray. I just look to see what is sensible. (Incidentally, the same issue of the *Journal* does carry an item (4) on confounding).

What the authors (1) treat as confounding factors are age (in broad age categories), sex, race, smoking (not relevant for the analysis on nonsmokers), three broad education groups, two broad occupation groups, and whether either parent smoked. Presumably, the factors adjusted for simultaneously in the analysis of passive smoking among nonsmokers are age, race, sex, and education.

But, somehow, I do not think of age as a confounding factor. Rather, it is a logical factor which must be taken into account in any reasonable analysis if one wants to come up with reasonable results. Much the same is true of race and sex, though I am less certain about level of education.

A truly confounding factor to my mind would be something like smoking and alcohol consumption. If heavy drinkers are also heavy smokers, sorting out their separate effects could be a problem. Anyway, if we are concentrating on passive smoking among non-

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smokers, then we are contrasting families with a single smoker against families where neither spouse smokes. And differences could exist between them. Thus we might ask: 1) Are their alcohol consumption habits the same? 2) What are the differences in their dietary habits? 3) How might they differ in age at first intercourse, frequency of intercourse, circumcision status of husband, etc.? 4) Are numbers of children or pregnancies and ages at first birth or pregnancy the same for single-smoker and nonsmoker families? 5) What true differences may exist in occupations leading to cancer?

These possible correlates of smoking practice might account for the observed differences reported in cancers of a variety of sites, and these are the true potential confounding factors, whether or not we are in a position to get at them. What Sandler et al. have taken as potential confounding factors are just the straightforward factors requiring adjustment that any reasonable epidemiologist would employ.

One particular thing strikes me about the Sandler et al. study. Passive smoking has been shown to double the risk of all cancers among nonsmokers, albeit true confounding factors have not been taken into account. But studies focusing on lung cancer among nonsmokers consequent on passive smoking have also come up with about the same doubling of risk. To other criticisms made of such other studies may be added that they may be overlooking true confounding factors.

The true criticism of passive smoking remains—it is an unpleasant burden to impose on the nonsmoker.

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RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is ironic that whereas a few of us agonize over the question of whether active smoking is a major cause of lung cancer others seem willing to believe that passive smoking causes an appreciable incidence of lung and other cancers.

Sandler et al. (1) purport to have studied cancer risk in relation to "passive smoking in adulthood." They did not. They studied cancer cases in active and nonactive smokers in relation, mainly, to the smoking habits of the spouse. Two broad aspects were considered: whether or not the spouse "smoked regularly at any time during their marriage"; and, for dose-response relations, "the number of years of marriage during which a spouse smoked," or "the average amount smoked by spouse." Also, the "nonexposed group consisted of persons married to nonsmokers and persons who never married."

The smoking habits of the spouse are, however, a very poor surrogate for passive exposure to cigarette smoke. Thus, Repace and Lowrey (2) have estimated that the typical workplace exposure in the United States is about four times the typical exposure in the home. Matsukura et al. (3) found in Japan that the mean (± SE) urinary cotinine excretion for 200 nonsmokers living with no smokers in the home was 0.51 ± 0.09 $\mu g/mg$ of creatinine; for 272 nonsmokers with smokers in the home it was slightly higher, at 0.79 ± 0.10 (same units), but not significantly so.

The assumption by Sandler et al. that the smoking status of the spouse is a useful measure of exposure to ambient cigarette smoke is, therefore, highly suspect. This doubt is borne out by their own study of lung cancer cases in which "... there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose ..." (1). The observed cancer associations were with the status of the spouse and not with exposure to cigarette smoke. That uncorrected confounding factors might have been present is further suggested by their finding of "statistically significant" associations "with several specific tumor sites ... including some which are not ordinarily regarded as smoking-related."

Assortative mating is a well established phenomenon that extends to the smoking habit (4) and hence we have to consider that the underlying factors leading to the choice of smoking/nonsmoking spouse might associate with the risk of certain cancers.

In principle, randomized trials can of course distinguish between causal, constitutional, and causal-plus-constitutional hypotheses of associations but they have yet to be conducted in connection with passive smoking. However, two important studies have been carried out, with randomization, in the context of active smoking (5, 6) and, because active smokers are inevitably passive smokers as well, the results of these trials are of immense importance not only to the findings of Sandler et al. but also to general theses about the carcinogenicity of mainstream and sidestream tobacco smoke.

We obtain the best available direct epidemiologic test of causal hypotheses by combining the results of the MRFIT in the United States (5) with those of the Whitehall Study in London (6). In the combined, low-smoking intervention groups some 56 cases of lung cancer (deaths in MRFIT, deaths and registrations in the Whitehall Study) were recorded in the total entry group of 7,142 men, a frequency of 0.78 per cent. For the combined, relatively high-smoking "usual care" groups the corresponding numbers were 53 in 7,169 or 0.74 per cent. Findings for all cancers other than lung cancer, several of which associate strongly with cigarette smoking, are astonishing. Some 88 cases, or 1.23

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per cent, were recorded in the combined low-smoking intervention groups but only 60, or 0.84 per cent, in the high-smoking usual care groups. Is smoking prophylactic? Does quitting smoking result in changes of life-style that cause cancer? Or is this finding a wild, but acceptable, random excursion?

We may not be entitled to estimate confidence limits from this post hoc scrutiny but the results of these methodologically reputable randomized trials cast grave doubts on the validity of orthodox claims about the hazards of smoking. These claims derive, in the main, from case-control and prospective studies of self-selected smokers, ex-smokers and nonsmokers which, by their very nature, can tell us much about association but nothing about cause. The study of Sandler et al. (1) does not even tell us about associations with passive smoking; it does, however, shed some interesting light on cancer associations with the smoking/nonsmoking status of the spouse.

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THE AUTHORS REPLY

Friedman (1) and Mantel (2) have expressed some concerns about our passive smoking findings that are concerns for us as well (3). We agree that it would have been useful to have information on a greater number of potential confounding variables. Unfortunately, when conducting a study of many cancers, it is difficult to do justice to individual sites because risk factors vary widely by site.

While the possibility of confounding variables exists, some of those suggested by Friedman and Mantel are not likely to explain our findings. We collected information on alcohol consumption, and adjustment for alcohol intake did not alter our results. Marijuana use is also not likely to be a factor, since most of our cases were older than 40 years of age and from largely poor and rural areas. Occupational exposures may be important, although it is difficult to see how occupation of the subject would be associated with spouse's smoking, other than as an indicator of social class. Simple stratification into white and blue collar occupations did not change our results (3), and there were too few individuals with the same job for a more detailed analysis to be meaningful. Information on reproductive factors would have been useful and should certainly be included in subsequent studies given the observed associations with cancers of the breast and cervix. Since many of the factors thought to increase the risk of cervical cancer are thought to decrease the risk of breast cancer, however, it is not clear that those factors could explain our finding of elevated risk at both sites. Sexual behavior of husbands may also be important in cervical cancer risk, but reports suggest that this does not entirely explain the observed associations with spouse smoking (4, 5).

Burch points out that the smoking habits of the spouse may be a poor surrogate for passive smoke exposure (6). Certainly total passive smoke exposure will be underestimated as Friedman's data suggest (7). However, Friedman's data and others suggest that individuals who live with smokers are likely to be more exposed to other people's cigarette smoke—either because they are more tolerant of other people's smoking or beause they are often exposed to other smokers when in the company of their smoking spouse (7, 8). Thus while smoking by spouse may only roughly reflect the amount of tobacco smoke exposure, it appears to distinguish the most exposed from the least exposed. Misclassification of exposure is likely to dilute any association rather than create a spurious association, unless only controls who are married to nonsmokers are also exposed at work. Furthermore, one fourth of our cases and controls (35 per cent of the females) were either housewives or unemployed, and thus likely to receive most of their smoke exposure at home. For these subjects alone, the odds ratio associated with spouse's smoking was unchanged at 1.6.

As Mantel has pointed out, past studies of cancer risk from passive smoke exposure have focused on lung cancer risk among nonsmoking women married to smokers. Our study was not designed to focus on this issue, and with only 22 lung cancers, and only two among nonsmokers, we can add little to clarify results from those studies.

While it may be surprising that strong relative risks were seen for sites not generally associated with cigarette smoking, we believe that such effects are possible. Studies indicate that passive smoking has a pervasive biologic effect (8-12), making the boundaries between "smoking related" cancer sites and other sites unclear. Some sites may be considered unrelated to cigarette smoke because risks are less dramatic than those for other sites, or because studies have not been done. While active smokers are also passive smokers, if an effect were due to some specific property of the side-

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stream smoke (e.g., increased concentration of chemicals or decreased particle size), it would be difficult to detect by comparing smokers to nonsmokers when the nonsmoking group also includes passive smokers. Alternatively, one could speculate that smokers, although at increased overall risk, may paradoxically be protected against some properties of cigarette smoke, possibly through stimulation of enzyme systems that metabolize carcinogens into less harmful compounds (13, 14). These same mechanisms may not be stimulated in nonsmokers who have different exposure to cigarette smoke.

We would not want to argue that a biologic pathway is established, but rather to say that a plausible pathway cannot be ruled out. Evidence suggests that passive smoking is not simply a lower dose of active smoking, and thus may need to be considered in a different light. Our findings are preliminary and need to be confirmed by other studies. Studies of individual cancer sites can evaluate potential confounding factors in more detail, and may be able to clarify the role of passive smoking.

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The Relation of Passive Smoking to Lung Cancer[1]

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ABSTRACT

To evaluate the role of passive smoking in the development of lung cancer among nonsmokers, data were pooled from three large incident case-control interview studies. Ninety-nine lung cancer cases and 736 controls never used any form of tobacco. Overall the adjusted odds ratio for lung cancer among nonsmokers ever living with a smoker was 0.8 (95% confidence interval, 0.5–1.3) rising to 1.2 among those exposed for 40 or more years. Persons living with a spouse who smoked cigarettes were at increased risk (adjusted odds ratio, 1.5; 95% confidence interval, 0.8–2.8). When adjusted for age and gender, there was a significant trend in risk with increasing amounts smoked per week by the spouse ($P = 0.05$) and with cumulative pack-years of exposure ($P = 0.03$). This effect was limited to females, especially older women whose husbands were heavy smokers. The elevated risk associated with spouse smoking was restricted to squamous and small cell carcinomas (odds ratio, 2.9; 95% confidence interval, 0.9–9.3), which provides additional evidence linking passive smoking to lung cancer.

INTRODUCTION

The respiratory effects of passive smoking among nonsmokers are of increasing concern; evidence suggests that such exposure may increase the incidence of bronchitis and pneumonia in early life (1) and decrease lung function among nonsmoking adults (2). Recent attention has centered on the possible risk of lung cancer among nonsmokers exposed to environmental tobacco smoke (3–6), although epidemiological studies have been limited by the small number of cases available for analysis. The National Cancer Institute has recently collaborated on three large case-control interview studies of lung cancer which included questions about passive smoking. One of these studies, conducted in Louisiana, showed an increased risk of lung cancer among ever-married nonsmokers who had a spouse that smoked (6). To increase our sample size for study, data on nonsmokers from all three case-control studies were pooled and analyzed.

MATERIALS AND METHODS

Persons reporting that they had never used any tobacco products (cigarettes, pipe, cigars, snuff, or chewing tobacco) were selected from three case-control interview studies of lung cancer conducted in Louisiana, Texas, and New Jersey. The methods used in each of these studies have been reported previously (6–9). Because all three studies were designed in collaboration with the National Cancer Institute, they were similar in many respects, as shown in Table 1. Medical and pathology records were abstracted to determine the final diagnosis of each case. All were incident primary lung cancer cases diagnosed between 1976 and 1982, with nearly 100% histologically confirmed. Personal interviews were conducted with the study subject or, if the subject was deceased or too ill to respond, with a surrogate respondent. Except where noted, the questions asked in each of the study areas were very similar.

Details regarding the source and level of passive smoking exposures varied according to study area (Table 1). Texas provided the least specific data by ascertaining only if any member of the subject's household smoked while the subject was either a child or an adult and the total number of years of that exposure. New Jersey, on the other hand, inquired about the smoking habits of each household member during the subject's youth and adulthood. Louisiana requested information regarding the smoking patterns of spouse, mother, and father, but not other members of the household. An estimate of the potential underreporting of passive smoking exposure in Louisiana is provided by the New Jersey control group; 6% of the nonsmoking males reported passive smoking originating from household members other than spouse, mother, or father.

The final study population abstaining from tobacco consisted of 99 histologically confirmed lung cancer cases and 736 controls. This represented 1.2% of all male cases and 9.1% of all female cases in the original study populations, as compared to 15.0% of the male controls and 44.9% of the female controls. The final data file included all variables that could be standardized across the study areas.

Several potential confounders were examined, including gender, race, age, study area, respondent type (subject or next of kin), any self-reported chronic lung conditions, employment in suspected high-risk industries, asbestos exposure, carotene and total vitamin A intake, and whether parents had smoked. Due to the limitation imposed by small numbers, age was dichotomized into two age groups (<63 years and 63+ years). Logistic analyses utilizing three age groups did not substantially alter the adjusted odds ratios reported here. High-risk industries were those identified in a recent review of case-control studies of lung cancer (10) and included fishing, construction, lumber manufacturing, chemical and petroleum manufacturing, primary metal manufacturing, and shipbuilding. Nutrient indices were calculated from the food frequency questions for each study area, using nutrient content in a typical portion of each food (11, 12). Low intake was defined as the lowest quartile of intake for controls from each area. Because of the comparability problem resulting from the selective exclusion of persons diagnosed with chronic lung conditions in Louisiana, analyses were duplicated excluding all persons who reported having a chronic lung condition in all three study areas.

Statistical methods included the calculation of crude ORs[3] for lung cancer risks associated with passive smoking exposures. Because of the small numbers in this analysis, ORs were calculated using a 0.5 cell adjustment (13). Dose-response effects were examined using a stratified analysis and the Mantel-Haenszel test for trend (14). The logistic model was used to exclude the effects of potential confounders and to obtain maximum likelihood estimates of the adjusted ORs (15–17). Decisions concerning parameter deletions for the model were based on the t statistics for significance of the individual parameter estimates, on changes in the value of the log likelihood, and on the goodness-of-fit of the model as measured by the comparison of predicted to observed ORs, both stratified and crude. Maximum likelihood 95% CIs for the ORs were calculated from the logistic model (15) or from the stratified analysis (18).

RESULTS

The data from all three study areas were merged to examine the effect of any passive smoking exposure in the home envi-

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

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Table 1 *Comparison of the three lung cancer case-control interview studies from which the nonusers of tobacco were selected*

	Study		
	Louisiana	Texas	New Jersey
Geographic area	29 Louisiana parishes	Gulf Coast of Texas	6 high-risk areas of New Jersey
Case diagnosis period	1979–1982	1976–1980	1980–1981
Study design	Hospital based	Population based	Population based
Racial groups included	Whites/blacks	Whites	Whites/blacks
Gender groups included	Males/females	Males/females	Males
Cooperation rate*			
Cases	91.8	91.5	87.7
Controls	93.5	87.9	73.4
No. of cases	1057 (M) 315 (F)	462 (M) 454 (F)	896 (M)
No. of controls	1073 (M) 320 (F)	451 (M) 464 (F)	1043 (M)
% histologically confirmed	97.8	100	100
Passive smoking data	Mother, father, spouse	Ever any household member	Specific household member
Nonusers of tobacco			
No. of cases	8 (M) 28 (F)	5 (M) 42 (F)	16 (M)
No. of controls	177 (M) 156 (F)	48 (M) 196 (F)	159 (M)

$* \dfrac{\text{No. of completed interviews} \times 100}{\text{No. of subjects contacted for interview}}$

ronment. There were slight variations in the passive smoking questions among the three study areas. However, since exposures from parents and spouse represented the bulk of passive smoking experienced by nonsmokers in the home, the decision to pool data on whether subjects had ever been exposed in the home environment appeared reasonable. There was no apparent increase in the risk of lung cancer among those who reported ever living with a household member who smoked (crude OR, 1.00; 95% CI, 0.64–1.56). Controlling for the strongest confounders (gender, age, and study area) reduced the OR to 0.84 (95% CI, 0.52–1.34). No significant differences were seen in the risks across sex and age strata or according to cell type of lung cancer.

A crude summary estimate of the duration of passive smoking exposure per individual was calculated for the Louisiana and New Jersey data by taking the maximum number of years that smoking was reported for mother or father and adding the years reported for spouse. In Texas, the reported value for years lived with any household member who smoked was used. In a stratified analysis, adjusted for age and gender, there was a slightly elevated OR of 1.24 (95% CI, 0.62–2.51) for those reporting 40 or more years of living with a smoker compared to 0.86 for <20 years and 0.82 for 20–39 years. These ORs were not significantly different from unity and showed no significant trend.

Since combining all known sources of passive smoking exposure might mask the effects of time period and intensity of exposure, the data were further analyzed with regard to specific sources of exposures. Because the Texas study lacked detailed data on the source and intensity of the passive smoking exposures, the remainder of the analysis was restricted to data on nonusers of tobacco from the Louisiana and New Jersey studies. The most complete information available for this combined population concerned the smoking patterns of the spouse. A total of 48 cases (22 males and 26 females) and 466 controls (318 males and 148 females) were ever-married nonusers of tobacco. **The crude OR for lung cancer associated with exposure to a smoking spouse was 1.87 (95% CI, 1.03–3.42) (Table 2).** Adjusting for confounding by gender, age, and study area reduced the odds ratio to 1.47. When controlling for age and gender, a significant upward trend was seen for increasing amount smoked per week by the spouse ($P = 0.05$) and cumulative pack-years of exposure ($P = 0.03$). Duration of spouse smoking, independent of amount, showed no consistent pattern.

Sex differences in risk were observed, with adjusted ORs of 1.96 for females (95% CI, 0.82–4.70) and 0.93 for males (95%

Table 2 *Odds ratios for lung cancer associated with a spouse smoking exposure among ever-married nonusers of tobacco in Louisiana and New Jersey*

Total Cases	Total Controls	Crude OR	Adjusted OR*
48	466	1.87 (1.03–3.42)	1.47 (0.76–2.83)
Amount spouse smoked/wk			
<140 cigarettes			1.36 (0.41–4.21)
140–279 cigarettes			1.31 (0.48–3.47)
280+ cigarettes			2.71 (0.84–8.52)
Significant trend ($P = 0.05$) for amount smoked			
Duration of spouse smoking exposure			
1–20 yr			1.73 (0.52–5.42)
21–30 yr			1.78 (0.60–5.10)
>30 yr			1.24 (0.42–3.53)
Pack-yr of exposure			
<20 pack-yr			0.78 (0.17–3.03)
20–35 pack-yr			1.90 (0.56–6.07)
>35 pack-yr			2.15 (0.84–5.40)
Significant trend ($P = 0.03$) for pack-yr of exposure			

* Overall OR (1.47) adjusted for gender, age, and study area in the logistic model (15–17); all other ORs adjusted for gender and age (18).

CI, 0.30–2.90). **This appears to reflect the greater frequency and amount smoked [redacted] smoking women compared [redacted]** In the control series, women were much more likely than men to have a spouse who smoked (48.0% compared to 18.2%), and the average exposure originating from the smoking spouse was greater for women than for men (mean pack-years, 40.6 for women and 27.1 for men). **The greatest risk was seen among older women (63+ years) whose husbands smoked at the highest intensity level (280 or more cigarettes/week) (OR, 5.14; 95% CI, 1.40–18.95). A dose-response relationship ($P = 0.02$) occurred among females with increasing pack-years of exposure from spouse smoking, with ORs ranging up to 2.99 (95% CI, 0.96–9.37) for females with greater than 35 pack-years of exposure.** The majority of nonsmoking males had 20–35 pack-years of exposure. Despite a suggestion of increased risk for men in this category (OR, 2.48; 95% CI, 0.52–10.23), the numbers were small, and no dose response was detected.

The ORs for lung cancer among nonsmokers were examined for the following histological types: adenocarcinoma; squamous and small cell carcinomas; and other cell types which included bronchioalveolar, undifferentiated, mixed, and not otherwise specified carcinomas, as well as carcinoids. As shown in Table 3, adenocarcinoma accounted for approximately one-third of the lung cancers in both sexes combined. A larger proportion

Table 3 Cell type distribution of lung cancer among ever-married nonusers of tobacco by sex

Cell type	Male No.	Male %	Female No.	Female %
Adenocarcinoma	7	31.8	9	34.6
Squamous and small cell carcinoma	9	40.9	5	19.2
Other	6	27.3	12	46.2
Bronchioalveolar carcinoma	2	9.1	3	11.5
Undifferentiated	2	9.1	3	11.5
Mixed	0	0	1	3.8
Not otherwise specified carcinoma	2	9.1	3	11.5
Carcinoid	0	0	2	7.7

Table 4 Cell type-specific ORs for lung cancer associated with spouse smoking exposure among ever-married, nonusers of tobacco in Louisiana and New Jersey

Cell type	Total Cases	Total Controls	Crude OR	Adjusted OR*
Adenocarcinoma	16	466	1.25 (0.44–3.51)	1.02 (0.33–3.16)
Squamous and small cell carcinoma	14	466	2.61 (0.93–7.32)	2.88 (0.91–9.10)
Other	18	466	2.11 (0.84–5.33)	1.31 (0.48–3.57)

* Logistic model included gender, age, and study area as potential confounders (15–17).

of squamous and small cell carcinomas was seen for men than for women, while other types of lung cancer were more common in women than men. The adjusted ORs (Table 4) associated with exposure to a smoking spouse varied from 1.02 for adenocarcinoma to 2.88 for squamous and small cell carcinomas.

The elevated risk for the squamous and small cell category was due mainly to the female cases in Louisiana; all five of the nonsmoking women with these cell types had spouses who smoked. The spouses of four of these five women smoked at a level greater than 25 pack-years. The men whose wives smoked showed a moderate increase in risk for squamous and small cell carcinomas (crude OR, 1.48; 95% CI, 0.34–6.39). Exclusion of all subjects who reported having a chronic lung condition did not alter the risk patterns.

Except for gender, age, and study area, no confounding was detected. The increased risks for lung cancer associated with passive smoking were not accounted for by race, respondent type, any self-reported chronic lung condition, employment in a high-risk industry, asbestos exposure, total vitamin A or carotene intake, or smoking by the parents. When the referent group was restricted to those persons reporting no passive smoking exposure from either a spouse or parent, the patterns of risk remained consistent with those we have presented.

DISCUSSION

The analysis of pooled data from three case-control studies in the United States suggested an increased risk of lung cancer among nonusers of tobacco who were married to smokers. Among women, this risk appeared to be dependent on the intensity of exposure to environmental tobacco smoke as estimated by the amount smoked by their husbands. Small numbers and relatively low exposures made it difficult to assess the role of passive smoking among tobacco-abstaining men whose wives smoked. While the overall ORs were not statistically significant, the finding of a dose-dependent risk of lung cancer among nonsmoking women is consistent with other observations in the literature. Hirayama (3) in Japan and Trichopoulos *et al.* (4) in Greece reported a significant increase in the lung cancer risk of nonsmoking women whose spouses smoked. Subsequently, the prospective survey of the American Cancer Society (5) found an elevated risk for passive smoking among nonsmoking women although the excess was nonsignificant and lacked a dose-response relationship. In our study the risk of lung cancer was not increased when passive smoking exposures from childhood and adulthood were examined collectively, emphasizing the need to obtain source-specific exposure data.

When the lung cancers were analyzed by cell type, the increased risk associated with passive smoking appeared restricted to squamous and small cell carcinomas, the types most closely linked to active smoking (19). This pattern suggests that passive smoking may contribute to the risk of lung cancer through mechanisms similar to those of active smoking, although sidestream smoke contains higher concentrations of certain compounds, such as nitrosamines, compared to mainstream smoke (20). In a recent case-control study by Garfinkel *et al.* (21), significant risks for both squamous cell carcinoma and adenocarcinoma were observed among nonsmoking women exposed to a spouse smoking at home, with the risks for squamous cell cancer being 3 times greater than for adenocarcinoma. Among nonsmoking Chinese women in Hong Kong, Koo *et al.* (22) found that the risk of passive smoking was greater for squamous and small cell cancers than for adenocarcinomas.

Although our analyses included nonsmokers from three large series of lung cancer, the small number of cases still precluded any definitive answers on the carcinogenic effects of passive smoking. Other limitations concern the difficulty in quantifying exposures from passive smoking derived from interview data and in detecting relatively low-level effects. Since our study was based on questionnaires, it was not possible to evaluate certain other exposures (*e.g.*, indoor radon daughter products) that may affect the risk of lung cancer among nonsmokers.

Our study was also limited by the assessment of passive smoking exposures experienced only in the home environment and by the use of a relatively crude measure of exposure. We assumed for this analysis that the amount and duration of a spouse's smoking habit approximated the passive smoking exposure realized by an individual at home. Fuller characterization of passive smoking should address the intensity of exposure, a function of the amount of time spent in close proximity to a smoker as well as the amount that individual smokes. In our study, the sex differences observed in exposure and risk suggest the desirability of continuing to focus attention on the nonsmoking wives of smokers, while encouraging the collection of data on workplace and other nonhousehold exposures to ambient tobacco smoke.

Whenever possible, future epidemiological studies should incorporate laboratory measurements of tobacco smoke constituents and by-products such as cotinine, the major metabolite of nicotine detected in body fluids. Among nonsmokers, a dose-response relationship has been observed between the levels of urinary cotinine and self-reported exposure to passive smoking (23, 24). Thus, while the available epidemiological data on nonsmokers suggest that passive smoking increases the risk of lung cancer, mainly of the squamous and small cell types, confirmation will probably require larger study sizes as well as more extensive and innovative assessment of exposure to environmental tobacco smoke.

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Respiratory Cancer in a Scottish Industrial Community: A Retrospective Case-control Study

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Summary
A retrospective case-control study was undertaken as part of an enquiry into possible causes of an epidemic of lung cancer in an industrial town in central Scotland. Relatives of the cases and controls answered a questionnaire which encompassed aspects of the social and occupational personal history of the deceased. Despite the length of time intervening between the period of mortality and this investigation, enough questionnaires were completed to allow the histories of the cases and controls to be usefully compared.

The results indicate that smoking and occupation contributed little to the aetiology of the outbreak of lung cancer in Armadale.

Introduction

In the small town of Armadale in central Scotland, an outbreak of primary lung cancer began in 1968 (Lloyd and Barclay, 1979; Lloyd et al., 1982). The mean standardized mortality ratio (SMR) for primary respiratory cancer from 1969–73 was the highest of all cities, burghs and landward areas in Scotland during that time (Lloyd and MacDonald, 1984). Within the town itself, many of the deaths from lung cancer formed a cluster near a source of air pollution—a steel foundry (Lloyd, 1978a, 1981). This cluster was statistically significant, with an SMR, based on Scottish rates, of 206 between 1968 and 1977. The cases of primary lung cancer had been identified initially by examining the diagnoses on the death certificates of the local parishes in the Registrar General's Office for Scotland. The validity of most of those diagnoses was confirmed later by obtaining supporting information from other sources of diagnostic data (Tyrrell and Lloyd, 1983).

During the earlier stages of the enquiry, the occupational and social backgrounds of the deceased were investigated on a preliminary basis, through the use of hospital case notes, death certificates and discussions with local doctors. No unusual features were identified which would have explained so many cases of lung cancer in such a short period (Lloyd, 1978b; Lloyd et al., 1982). Nevertheless, to test the hypothesis that the cluster of lung cancer might be causally linked to occupation and smoking habits, it was considered essential to undertake more detailed enquiries into the social and occupational backgrounds of the deceased. We decided to construct a questionnaire which would be answered by relatives of the deceased in the form of a retrospective case-control study. Most of the questions concerned details of the smoking habits and occupational experiences of the deceased with additional questions covering personal and familial histories of related lung disease and cancer, and the residential histories.

Methods

The period covered by the study was 1968–74, when the SMR for the town had been found high. The cases were residents of Armadale who had died during 1968–74 with the diagnosis of primary lung cancer on the death certificate. The controls were chosen from a list of residents of Armadale who had died from any cause other than lung cancer, during the same period. Preliminary work had shown that this width of diagnostic frame was necessary to allow matching for the social characteristics in this small population. The cases were computer-matched consecutively for sex, age at death ± 10 years, year of death ± 5 years, and by social class I–V. Anticipating the problem of failure to trace some controls, reserve controls were obtained for as many cases as was possible.

Ethical permission was obtained at district and area health board levels for tracing and interviewing next-of-kin or other relatives (hereafter referred to collectively as relatives). The agreement of the local family doctors was also obtained.

Using the experience gained from a pilot study of a similar questionnaire within an occupational workforce elsewhere, a final questionnaire was constructed. Since the major areas of interest were the tobacco habit and occupational history of the deceased, most of the questions covered details of those areas. For smoking history, questions included the average, minimum and maximum numbers of cigarettes smoked daily, the age of starting smoking, the number of years of that habit, the use of pipes and cigars and filter cigarettes, the brand name of the tobacco used (from which the tar content was estimated), the inhalation practice, the habit of smoking at work, and exposure to passive smoking at work and at home. There was also a question on the certainty with which this information was given. For occupational history, questions covered occupations since leaving school, and exposure to specified chemical and physical factors; details were requested of any time spent at particular types of work within the coalmining and steel foundry industries. For the previous medical history of the deceased, questions covered experience of non-malignant respiratory diseases. For the familial medical history, the questions also included cancers and coronary heart disease. The questions on place of residence covered addresses since 1940. These addresses were subsequently assigned to Zones A–E, (*see Fig.* 1), which were aggregates of enumeration districts of the town at the 1971 census and which had been used previously in epidemiological investigations.

Questions also covered residential proximity to industrial sources of environmental air pollution, and the degree to which that pollution inconvenienced the individual concerned. The type of fuel used normally for

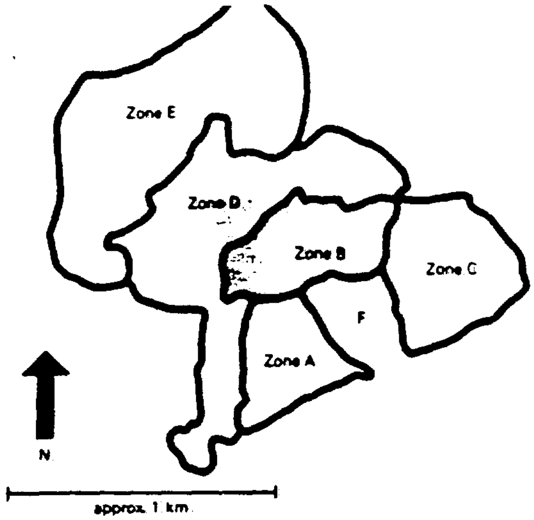

Fig. 1. Zone map of Armadale. Zone A: west of foundry; Zone B: north of foundry; Zone C: east of foundry; Zone D: intermediate; Zone E: distant; F: foundry.

Table I. Age at death of cases and controls

	Age group					
	30–39	41–49	50–59	60–69	70–79	80+
Cases	2 (5%)	1 (2%)	4 (10%)	15 (36%)	14 (33%)	6 (14%)
Controls	0 (0%)	2 (5%)	6 (14%)	15 (36%)	15 (36%)	4 (10%)

heating and cooking was investigated. Finally, various combinations of factors were examined to try to identify signs of interaction between them in promoting the elevated mortality from lung cancer.

The questionnaire was administered to the nearest surviving relative of the deceased, by one of two interviewers. To avoid interviewer bias, the interviewers were not told whether the person they were interviewing was a relative of a case or of a control. The relatives were traced mainly with the assistance of the local general practitioners and other staff at the only group practice in the town. Where they were unable to identify surviving relatives still living in the area, they were often able to supply names and addresses of friends who knew where the relatives could be found. Other sources used for tracing relatives were a local minister, and, for some of the more unusual names, the local telephone directory.

For those cases and controls whose relatives could not be contacted, other sources of information were used to ascertain only the location of the last known address.

The information derived from the questionnaire was subjected to frequency analysis; and for many exposures, the relative risks and their 95 per cent confidence limits were used to test the null hypothesis that the answers of the cases and controls did not significantly differ from each other.

Results

General

The interviews were carried out between November 1982 and March 1984.

Of a possible 137 relatives on the list of interviewees, 103 (75 per cent) were traced and interviewed. Nineteen controls were subsequently eliminated: either they were the 'reserve' controls of cases for which a matched control had already been obtained, or the cases to which they were matched had no known relatives—the relatives having migrated to an unknown location or abroad. The final total of interviews used for the analysis of the data was 84: 42 cases, each with one matched control.

Of the 42 cases of primary lung cancer obtained for the analysis, 35 were males. The age at death of the cases ranged from 37 to 86 years; those of the controls were from 47 to 84 (*Table I*). Because the lapse of time between the year of death and this study taking place was up to 18 years, it was found that many of the spouses of the cases and controls had died. Hence the largest group of informants was the daughter/son group, the second largest being the husband/wife group (*Table II*). Thus, information about 30 of the cases and 32 of the controls was obtained from a close relative (spouse, sibling, son or daughter).

Smoking History

There were no statistically significant differences between the answers of the cases and controls in any of the questions (*Table III*).

More cases than controls were found for those who had ever smoked, for cigarettes only, cigar/pipe smokers and for smokers of plain cigarettes; for small and large numbers of cigarettes smoked, for high tar content of cigarettes; and for inhaling practice.

More controls than cases were found for non-smokers and smokers of filter cigarettes; for medium (15–29) consumption of cigarettes; for being permitted to smoke at work; and for passive smoking both at work and at home.

The cases started smoking at an earlier age (18·7 years) and continued the habit for longer (45·6 years).

There was less certainty about the smoking habits of the controls than about the habits of the cases.

Occupational history

The differences between the number of cases and controls employed in the major industries of the town (coal mines, steel foundry, brickworks), were not statistically significant (*Table IV*). Slightly more cases than controls

Table II. Relationship between respondent and deceased

	Husband/wife	*Son/daughter*	*Brother/sister*	*Nephew/niece*	*Grandchild*	*In-laws*	*Other*
Cases	13 (31%)	13 (31%)	4 (10%)	7 (17%)	1 (2%)	3 (7%)	1 (2%)
Controls	8 (19%)	17 (41%)	7 (17%)	7 (17%)	1 (2%)	2 (5%)	0 (0%)

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Table III. Characteristics of the smoking history of cases and controls

Category	Characteristic		Cases	Controls	Relative risk*	95% confidence limits
	Never smoked		3	8	1·0	
	Cigarettes only		28	26	2·87	0·68–11·94
	Cigarettes and pipe or cigar		4	4	2·67	0·39–18·16
	Pipe or cigar only		7	4	4·67	0·76–28·47
Ever Smoked: cigarette/pipe/ cigar	Smokers		39	34	3·06	0·75–12·44
	Filter cigarettes		6	8	1·0	
	Plain cigarettes		19	12	2·11	0·59–7·61
	Plain and filter		5	4	1·66	0·31–9·01
Mean quantity smoked for duration of habit	1–14 Cigarettes/day		11	7	1·0	
	15–29 Cigarettes/day		10	13	0·49	0·14–1·73
	30+ Cigarettes/day		9	8	0·72	0·19–2·78
Tar content (estimated from brand name)	Low-medium tar		5	7	1·0	
	High tar		21	14	2·1	0·55–7·95
Includes cigar/ pipe smokers	Inhaling practice	Yes	26	24		
		No	3	6		
	Permitted to smoke at work	Yes	10	13		
		No	25	19		
Continual exposure to passive smoking	At work	Yes	10	15	0·56	0·21–1·50
		No	25	21	1·0	
	At home	Yes	32	34	0·84	0·29–2·45
		No	9	8	1·0	
(in years)	Age started smoking		$\bar{x}$ 18·7	19·2		
			SD 9·1	8·9		
(in years)	Duration of habit		$\bar{x}$ 45·6	43·7		
			SD 12·7	12·2		
Reliability of information	Very reliable		3	3		
	Fairly reliable		22	14		
	Some idea		6	7		
	Uncertain		3	4		
	Guess		3	2		

* Relative risk = 1·0 identifies baseline category.

had worked in the coal mines at some time, but fewer had worked in the local steel foundry. Almost equal numbers of cases and controls had worked in the local brickworks. All other occupational groups contained negligible numbers of both cases and controls. Some individuals had worked in more than one industry.

When coal mining and foundry work were categorized according to subgroups of occupation, the biggest difference between cases and controls was for the moulder/coremaker group of foundry workers, with 1 case and 5 controls. For exposure to chemical agents, there were no significant differences between cases and controls.

Personal and familial medical histories

Considerably more cases than controls were reported to have had a history of bronchitis (*Table V*). This difference was statistically significant, with a relative risk of 3·71 and 95 per cent confidence limits of 1·19–11·58.

Due to the difficulties with recall experienced by the relatives, it was not possible to obtain a reliable or comprehensive history of chest disease or of all types of cancer in the families of cases and controls. However, in the data available there were no significant differences between the numbers of relatives of cases and controls for the histories of asthma, lung tuberculosis, and all cancers.

Only slight differences between cases and controls were noted for the types of fuel used for domestic cooking and heating (*Table VI*).

Residential history

Most of the cases and controls had been lifelong residents of Armadale; only 5 cases and 8 controls had ever lived outside the town. Of those who had resided outside Scotland, 4 were cases (2 in the USA, 1 in Australia, 1 in Newfoundland) and 6 were controls (3 in England, 1 in the USA, 1 in France, 1 in Poland).

The modal number of addresses for each person was 2; 16 cases and 17 controls had that number. No person had lived in more than 4 addresses.

include persons who ever worked in the industry):

Category	Characteristic		Cases	Controls	Relative risk*	95% confidence limits
Working history	Other occupations		17	24	1·0	
	Coal mining		21	17	1·74	0·71–4·25
	Steel foundry		9	13	0·98	0·34–2·82
	Brickworks		6	7	1·21	0·35–4·26
Exposure to	Coal dust	Yes	20	15	1·78	0·69–4·60
		No	15	20	1·0	
	Sand, silica, cotton or mineral fibres	Yes	4	4	1·0	
		No	31	31	1·0	
	Metal dust/fumes	Yes	7	7	1·0	
		No	28	28	1·0	
	Direct and intense heat	Yes	2	2	1·0	
		No	33	33	1·0	
Mine workers only	Surface and/or general		5	4	1·0	
	Faceworker		13	11	0·95	0·20–4·44
	Surface and face-worker		3	2	1·2	0·13–10·99
Foundry workers only	Moulder/coremaker		1	5		
	Furnaceman		1	0		
	Sandblaster		2	0		
	Smith/forger		0	1		
	Specific occupation unknown		4	1		

* Relative risk = 1·0 identifies baseline category.

Table V. Characteristics of the medical history of cases and controls

Category	Characteristic		Cases	Controls	Relative Risk*	95% confidence limits
Personal medical history	Bronchitis	Yes	14	5	3·71	1·19–11·58
		No	27	35	1·0	
	Pneumonia	Yes	6	5	1·21	0·34–1·47
		No	35	35	1·0	
	Pneumoconiosis	Yes	10	7	1·52	0·52–4·49
		No	31	33	1·0	
	Unspecified respiratory	Yes	25	21	1·41	0·58–3·40
		No	16	19	1·0	
Family medical history	Coronary heart disease		11	17	1·0	
	Asthma		1	3	0·51	0·05–5·56
	T.B.		2	0		
	Lung cancer		2	3	1·03	0·15–7·19
	Other cancers		8	3	4·12	0·89–18·88
	Pneumoconiosis		4	8	0·64	0·16–2·61

* Relative risk = 1·0 indentifies baseline category.

Within Armadale, there were no statistically significant differences between numbers of cases and controls who had ever lived in the various zones (*Fig.* 1). More cases than controls had ever lived in Zone A, the area with the cluster of lung cancer deaths (*Table VII*). When the period 1965–74, (i.e. just before and during the time when the SMRs for lung cancer were abnormally high) was examined as a separate unit, the difference between the numbers of cases (12) and controls (8) who had lived in Zone A was even greater (*Table VIII*). The only other zone where the cases exceeded controls was Zone C, directly east of the foundry (*Fig.* 1); during the period 1965–74, 6 cases and 3 controls had lived there.

Table VI. Type of fuel or power used for domestic heating and cooking

	Gas	Coal	Electric	Coal and other
Heating				
Cases	2 (5%)	35 (83%)	1 (2%)	4 (10%)
Controls	1 (2%)	35 (83%)	3 (7%)	3 (7%)
Cooking				
Cases	32 (76%)	6 (14%)	2 (5%)	1 (2%)
Controls	33 (77%)	4 (10%)	3 (7%)	2 (5%)

Fifteen lung cancer cases had no known relatives and were therefore *not* included in the 42 cases in this study.

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Table VII. Ever lived in each zone

	Zones A	B	C	D	E
Cases	14	11	7	17	7
Controls	11	12	4	21	7

Table VIII. Dates of residence in zones A and C

	1940–64	*1965–69*	*1970–74*
Zone A			
Cases	2	11	1
Controls	3	7	1
Zone C			
Cases	0	3	3
Controls	1	1	2

Table IX. Location of last known address of cases and controls whose relatives could not be contacted

	A	*B*	*C*	*D*	*E*
Cases	3	3	1	6	2
Controls	8	6	2	9	5

However, they were matched to 30 controls (some other cases having a reserve control). When their last known addresses were plotted by zone, there were no significant differences in distribution between cases over controls (*Table IX*). Thus there was no bias in the geographical distribution of the cases included in the study.

Of those who were conscious of a neighbouring source of environmental air pollution, the only major difference between numbers of cases and controls was for the combination of steel foundry and brickworks (*Table X*). But the cases did not complain of resulting inconvenience much more than did the controls.

Various combinations of factors, including residence in Zone A were analysed (*Table XI*), but no significant signs of interaction were found which might have contributed strongly to the elevated mortality from lung cancer. The combination of residence in Zone A during 1965–74 and a history of bronchitis showed the greatest difference. A similar difference was found for the combination of heavy smoking (more than 29 cigarettes daily and middle-to-high tar content) and a history of bronchitis. In all comparisons, however, the numbers were too small to allow a reasonable opportunity of finding statistical significance.

Discussion

Despite the long time between the increased incidence of lung cancer and the interviews with the relatives, the

Table X. Proximity to pollution source

Comment	*Variable*	*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
	Steel foundry only	11	11		
Applies only when residence was within ½ mile of the industry	Gas works and foundry	1	1		
	Brickworks, gas and foundry	1	4	0·50	0·01–27·11
	Brickworks, foundry	20	13	3·08	0·86–11·07
	Steelworks, brickworks and coal mine	4	3	2·67	0·42–16·83
Outwith ½ mile proximity		5	10	1·0	
Awareness of atmospheric pollution	Yes	15	12		
	No	27	30		

* Relative risk = 1·0 identifies baseline category.

Table XI. Combinations of factors (3-way tables)

Factors:—
1. Resident in zone A between 1965–74
2. Heavy smoker, i.e. over 29 per day, and middle or high tar
3. Ever worked as miner
4. Ever worked in foundry
5. History of bronchitis

	Cases	*Controls*
1 and 2	2	3
1 and 3	4	3
1 and 4	5	4
1 and 5	4	0
2 and 3	6	6
2 and 4	3	2
2 and 5	6	2
3 and 4 and 1	0	0
3 and 4 and 2	3	0

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... of contacts made and the responses at interview allowed a comprehensive picture to be gained of the occupational and social backgrounds of cases and controls. This experience was similar to that reported in an investigation of asbestos-related mesothelioma (Finlayson et al., 1971).

In general the occupational experiences of both cases and controls were very similar. Some epidemiological studies have suggested that workers in ferrous industries are at a greater risk of dying from lung cancer than persons in the general population; the risk of lung cancer has been related especially to exposure to 'hot metal', with moulders particularly at risk (Morrison, 1957; Hueper, 1966; Radford et al., 1976; OPCS, 1978; Wall, 1980). However, this present study confirmed the results of preliminary work (Lloyd et al., 1982) in finding no evidence to support the association of lung cancer with foundry work in general; nor was an association found with hot metal exposure or with moulding in particular. There were no reports of asbestos or radon exposure. No statistically significant differences were found between the numbers of cases and controls exposed to coal, dust, sand, silica, direct and intense heat from industrial furnace, metal dusts, or fumes from petroleum and its products. Hence, occupational experiences did not appear to have contributed in any important way to the elevated mortality from lung cancer in Armadale. (The similarity between the numbers of cases and controls having a coal mining history and an exposure to coal dust indicated the reliability of the respondents' answers, at least in that context of occupational experience.)

Because the most important cause of lung cancer is known to be cigarette smoking, the questions about smoking habits were very detailed. However, since this study relied on individuals remembering what their relatives were doing up to 15 years previously, we could not obtain as full and comprehensive an account of the smoking habits of the deceased as could be expected in more favourable circumstances. For instance, while it was fairly easy to obtain a figure for the amount of tobacco smoked daily, the respondents found it far more difficult to provide information concerning inhaling practice, and often had difficulty with brand names. However, an examination of the information about the amount, the duration of habit, the types of cigarette smoked, the opportunity to smoke at work, and about passive smoking, showed no significant differences between cases and controls in any factor. For some risk factors, there was an excess of controls. The biggest difference between the groups (19 cases and 12 controls having smoked plain cigarettes) could have been a consequence of the greater amount of missing and uncertain information found with the control group.

When considering familial medical histories it was noted that a history of lung cancer in the close family was as infrequent amongst the cases as amongst the controls. A family history of all other cancers was more frequent with the cases than with controls, but the small numbers in both groups make this finding difficult to interpret.

The high frequency of a history of bronchitis amongst the cases, which was the only statistically significant difference between cases and controls, is consistent with evidence that bronchitis and lung cancer are both associated with air pollution, as well as with cigarette smoking.

Indoor air pollution from cooking and heating appliances has been suspected as a pathogenic factor for respiratory disease (Florey et al., 1979; Lende, 1980). No significant difference in the use of such appliances by cases and controls was apparent in this study. The relatively small difference between numbers of cases and controls who had ever lived in Zone A, an area which was subject to relatively high air pollution (Yule and Lloyd, 1984; Gailey and Lloyd, 1983, 1985) and where an excess of lung cancer had been discovered (Lloyd, 1978a), might have resulted from our inability to eliminate from our controls all those whose deaths could have been linked with the air pollution through causes other than lung cancer. However, because of the small size of the town and hence the small number of deaths each year, deaths from all other causes had to be included as potential controls in order to allow the other characteristics of the cases to be matched. Nevertheless, despite this difficulty in the design of the study, the findings were consistent with the statistically significant excess of cases observed previously in an area close to the site of a polluting industry (Lloyd et al., 1982; Lloyd, 1982).

In summary, this study demonstrated that social and occupational factors were probably not of importance in the outbreak of lung cancer in Armadale during 1968–74. Hence the hypothesis that environmental air pollution might have played a significant aetiological role was not invalidated. The study also illustrated the practicability of undertaking a retrospective study covering a wide range of occupational and social factors by means of questionnaires given to relatives of people who had died up to 15 years before the start of the study.

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NOTE: --
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EFFECT OF PASSIVE SMOKING IN LUNG CANCER DEVELOPMENT IN WOMEN IN THE NARA REGION

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Translation from Japanese

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EFFECT OF PASSIVE SMOKING IN LUNG CANCER DEVELOPMENT IN WOMEN IN THE NARA REGION

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Introduction

It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis has become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women.

1. Subjects and Method

1) Subjects

The subjects were 25 women with lung cancer who were admitted to our department. They averaged 67.5±8.8 years of age. Based on histology there were 7 cases of squamous cell carcinoma, 5 of small cell carcinoma and 13 of adenocarcinoma. The age averages for the above groups were 71.4±7.8, 66.2±9.3 and 65.8±9.0 years, respectively. As controls, 50 cases of non-malignant hospitalized patients matched for sex and age (within 2 years) were selected. Their age average was 67.6±8.5 years.

2) Items of examination

To gather data on active and passive smoking (current and past) and familial accumulation of cancer, detailed questioning was conducted regarding personal history, concomitant disease, exposure to atmospheric pollution, stress, occupation, obesity, alcohol consumption and other items with the patient herself and with the family. Passive smoking was defined as exposure to smoking more or less daily through living with a smoker, and the amount was defined as the number of cigarettes smoked by the smoker each day multiplied by the number of years of exposure. Familial accumulation was based on occurrence or absence of malignancy in relatives to the 3d degree. Comparison with controls was made on the basis of significance of difference and relative risk regarding smoking and familial factors for each histologic type of tumor. Squamous cell carcinoma and small cell carcinoma which are regarded as

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having an intimate relation to smoking were grouped together.

2. Results

1) Squamous cell carcinoma (Table 1)

There were 4 patients who were active smokers out of 7. Passive smoking was experienced in all, but 6 were currently exposed while 5 had a history of exposure. Three reported exposure at an early age. Familial accumulation was observed in 4 cases, of which 3 were lung cancer, a high incidence, while 2 were gastric cancer. General history included one case of ovariectomy and 2 cases of ulcer of the digestive tract. Four had experienced atmospheric pollution and 3 reported stress. In the 3 non-smokers (cases 5, 6 and 7), passive smoking and familial cancer both occurred. These patients were the most elderly.

2) Small cell carcinoma (Table 1)

Four of 5 were active smokers. Passive smoking occurred in all 5, these all being exposed currently, while one case had a history of passive smoking and one could not be determined regarding this information. Familial accumulation was found in 4 cases, 3 being cases of gastric cancer, a high incidence. As for personal history, there was one case each of uterine cancer and hysterectomy and one case of breast cancer. Exposure to atmospheric pollution occurred in 2 and stress in 4. In the one non-smoker (case 5) there was intense passive smoking. The individual had a history of surgery for breast cancer, and her two younger sisters had had breast cancer and uterine cancer (individually). This group of patients averaged 5 years younger than the cases of squamous cell carcinoma.

3) Adenocarcinoma (Table 2)

There was not a single active smoker out of 13, but all had been exposed to passive smoking, 12 out of 13 being currently exposed. There were 10 out of 11 who had a history of passive smoking, 8 since early childhood. Familial incidence of cancer was present in 11 out of 13, two being lung cancer, 7 gastric cancer, 4 esophageal cancer and 2 colon cancer. Three had uterine fibroid and 1 had undergone hysterectomy. There were 2 cases of respiratory disease. Exposure to atmospheric pollution occurred in 5, and stress in 4. In 11 out of 13 there was passive smoking along with familial cancer. In the other two there was intense passive smoking in one and passive smoking plus pulmonary tuberculosis in the other.

4) Controlled studies (Tables 3, 4 and 5)

Regarding passive smoking (Table 3), there was a significant difference between lung cancer cases and controls in the amount of exposure ($p<0.05$), although no definite difference could be observed according to tumor cell type. When the cases were grouped into those who had been exposed up to the present time, those who had been exposed in the past and those who had been exposed since early childhood,

Table 1. Squamous cell carcinoma and small cell carcinoma of the lung in women.

A. Squamous cell carcinoma.

	Age	Active smoking	Passive smoking Past	Passive smoking Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. T.O.	78	500	son +	father, loose tob husb 1,600 cigs	—	pyelitis	hyper-tension	+	house-wife	—	husband: gastric ca. TB
2. M.R.	57	853	husb 1,653 son 400 cigs	younger bro. loose tob	—	excision of ovary	—	—	house-wife	—	
3. N.O.	70	330	husb 400 cigs	—	Aunt (LC)	Gastric ulcer	Lumbar deforma.	—	house-wife	—	
4. K.S.	70	300	—	father loose tob husb 360 cigs	—	Lumbar herniat.	Hyper-tension	—	house-wife	+	
5. T.N.	68	—	husb 960 cigs	father 400 cigs	older bro (LC) Yng (LC) sister	Injury rt. hand	—	+	plastic industry	—	
6. T.S.	79	—	husb +	—	Mother (GC) old. (LC) bro.	duodenal ulcer	Neuro-genic cystitis	+	house-wife	+	
7. K.N.	78	—	son 1,600 cigs	husb 450 cigs	father (GC)	appendic. hypo-tension	Parkins. angina pectoris	+	pawn-broker	+	

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Table 1. (con't) B. Small cell carcinoma (women)

	Age	Active smoking	Passive smoking Past	Passive smoking Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	67	350	son 100 cigs	—	mother (GC) old (RC) sister	uterus ca hepatit. gall stone	cardiac insuff.	—	house-wife	+	
2. E.Y.	50	625	husb +	—	father (GC)	hysterec. gast.uld lymph node TB	—	+	family factory	+	
3. T.H.	70	500	husb + daught +	--	old bro (GC) yng bro (?C)	gall stone cere. embol	—	—	house-wife	+	
4. F.M.	72	300	husb 370 cigs son 600 cigs	?	—	pul TB bronch. asthma	—	+	house-wife	-	
5. T.T.	72	—	daughter cig120 grand 550 child cigs	fath. 320 uncle300 husb 640 cigs	yng sis(MC) yng(UC) sis	breast ca	—	—	teacher	+	divorced

Table 2. Adenocarcinoma in women

A. Adenocarcinoma

	Age	Active smoking	Passive smoking Past	Passive smoking Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	73	—	son +	mother pipe husb 200 cigs	old sister (LC)	pleurisy	hyper-tension	+	camera store	—	
2. Y.M.	75	—	husb 1,040 cigs son +	?	old bro (EC)	traffic accident	—	—	agri-cult.	—	
3. Y.M.	66	—	husb 700 cigs	father +	mother (CC)	uterine fibroid	hyper-tension atr. fibril.	—	house-wife	+	depression
4. T.M.	77	—	son 1,050 cigs	father + husb 125 cigs	old sis (GC)	—	hyper-tension	—	house-wife	—	
5. K.M.	71	—	husb 470 cigs	father-pipe mother-pipe	mother (GC) old bro (LC)	hysterec. herpes	—	—	agri-cult.	—	
6. Y.T.	76	—	son 310 cigs	father + grandparent 300	fath (RC) moth (GC)	fracture of vertebra	hyper-tension	—	agri-cult.	—	
7. S.W.	66	—	son 400 cigs	—	mother (EC) old brother (GC)	wrist fracture	—	furnace (soot)	fish market	±	
8. Y.F.	50	—	—	father 150 husb 200 cigs	grand-fath (EC) aunt (GC)	uterine fibroid hernia	—	—	house-wife	—	
9. T.M.	60	—	husb 600 son 180 cigs	?	uncle (GC) aunt (LyC) child (MLy)	—	rheuma-tism	—	house-wife	+	
10. H.O.	49	—	+ at work	husb 480 cigs	cousin (GC) cousin (?C)	—	—	+	coffee shop	+	
11. H.Y.	64	—	husb 700 cigs	father pipe	mother (EC)	uterine fibroid lung absc.	—	+	house-wife	—	2
12. S.S.	68	—	son 580 son 100 cigs	husb 800 uncle 200 yng bro 180 cigs	—	—	hyper-tension	—	agri-cult.	—	husband: lung ca
13. T.I.	61	—	husb 800 cigs	fath 600 cigs	—	—	pulmonary TB	+	agri-cult.	—	pul (+) infection

the greatest influence was found to be that of present exposure, with a significant ($p < 0.05$) difference from the controls. Some differences were also seen in cases of all lung cancers and of adenocarcinoma who had history of passive smoking.

Among active smokers (Table 4), there was no difference between the lung cancer group and controls, but the combined number of cases of squamous cell carcinoma and small cell carcinoma was significantly ($p < 0.01$) higher in active smokers compared with non-active smokers, while the incidence of adenocarcinoma actually had a negative correlation with active smoking.

Among passive smokers (Table 4), when compared 1:1 with controls who were also non-active smokers, no significance was observed in the history of exposure, overall, present or past, but the ratio was virtually the same as that when active smokers were included (Table 3). Some difference, however, were observed for overall lung cancer and adenocarcinoma cases with history of past exposure to smoking.

When cumulative family incidence of cancer (Table 5) was investigated, it was found to create a significant ($p<0.001$) difference between lung cancer cases and controls, the association being especially strong with adenocarcinoma, indicating that family incidence of cancer was an important factor in this type of cancer.

When smoking and familial cancer were combined (Table 5), the results were not significant with active smoking, but significant with passive smoking. The increase in risk when familial cancer and passive smoking were combined over that of familial history alone was as follows: All lung cancers + present exposure to passive smoking, x11.7; all lung cancers + past exposure to passive smoking, x 10.0; all lung cancers + active or passive smoking, x17.3; squamous cell carcinoma + small cell carcinoma + present exposure to passive smoking, x7.0; squamous cell carcinoma + small cell carcinoma + active or passive smoking, x40.8; and adenocarcinoma + past exposure to passive smoking, x26.7.

3. Discussion

The question of lung cancer development in non-smokers exposed over extended periods to smoking by others in the family and at the place of work has become a social concern not only in the United States but also in Japan.

In the present study, we gathered detailed information on the history of illness and family background in 25 cases of lung cancer in women, and investigated the relations among passive smoking, active smoking and familial incidence of cancer. The subjects were residents of Nara Prefecture, most of them housewives or women engaged in farming. The passive smokers in this study were all living with one or more smokers, therefore presumably exposed to passive smoking daily from at least

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	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Passive smoking (Total)	25/25 (100)			40/50 (80)	<0.05	13.2
		12/12 (100)		17/24 (71)	<0.1	10.7
			13/13 (100)	23/26 (88)	NS	—
Passive smoking (At present)	23/25 (92)			32/50 (64)	<0.05	6.5
		11/12 (92)		14/24 (58)	<0.1	7.9
			12/13 (91)	18/26 (69)	<0.1	5.3
Passive smoking (In the past)	16/22 (73)			20/44 (45)	<0.1	3.2
		6/11 (55)		9/22 (41)	NS	—
			10/11 (91)	11/22 (50)	<0.1	10.0
Passive smoking (In childhood)	13/22 (59)			20/44 (45)	NS	—
		4/11 (36)		9/22 (41)	NS	—
			8/11 (73)	11/22 (50)	NS	—

( ) : %. NS: not significant

Table 3. Passive smoking and lung cancer in women (controlled study I).

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	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Active smoking (+)	8/25 (32)			14/50 (28)	NS	—
		8/12 (67)		4/24 (17)	<0.01	10.0
			0/13 (0)	10/26 (38)	<0.05	0.06
Passive smoking (at present)	17/17 (100)			14/17 (82)	NS	—
		4/4 (100)		3/4 (75)	NS	—
			13/13 (100)	11/13 (85)	NS	—
Passive smoking (in the past)	16/17 (94)			17/17 (71)	NS	—
		4/4 (100)		3/4 (75)	NS	—
			12/13 (92)	9/13 (69)	NS	—
Passive smoking (in childhood)	13/15 (87)			7/15 (47)	<0.1	7.4
		3/4 (75)		2/4 (50)	NS	—
			10/11 (91)	5/11 (45)	<0.1	12.0

( ): %. NS: not significant

Table 4. Passive smoking and lung cancer in women (controlled study 2).

	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Cumulative familial cancer	18/25 (72)			13/50 (26)	<0.001	7.3
		7/12 (58)		7/24 (29)	NS	—
			11/13 (85)	6/26 (23)	<0.001	18.3
Active smoking + familial cancer	4/25 (16)			4/50 (8)	NS	—
		4/12 (33)		2/24 (8)	NS	—
			0/13 (0)	2/26 (8)	NS	—
Passive smoking (at present) + familial cancer	18/25 (72)			9/50 (18)	<0.0001	11.7
		7/12 (58)		4/24 (17)	<0.05	7.0
			10/13 (77)	5/26 (19)	<0.001	14.0
Passive smoking (in the past) + familial cancer	11/22 (50)			4/44 (9)	<0.001	10.1
		3/11 (27)		2/22 (9)	NS	—
			8/11 (73)	2/22 (9)	<0.001	26.7
Active or passive smoking + familial cancer	23/25 (92)			20/50 (40)	<0.001	17.3
		12/12 (100)		9/24 (38)	<0.005	40.8
			11/13 (85)	11/26 (42)	<0.05	7.5

( ) : %. NS: not significant

Table 5. Familial incidence of cancer and smoking in relationship to lung cancer in women (Controlled study 3).

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the evening until the following morning.

It was found that present exposure to passive smoking was more influential than past exposure; that active smoking had a fairly marked effect on the development of squamous cell carcinoma or small cell carcinoma; and that in these histologic types, current (up to the present time) exposure to passive smoking had a marked effect. On the other hand, there was virtually no effect of active smoking on the development of adenocarcinoma,but there was suspicion of the effect of past or present exposure to smoking in this type of tumor.

The effect of passive smoking should be considered qualitatively and quantitatively. In assessing the qualitative effect of passive smoking, the following items should be considered: The amount of carcinogenic material in secondary smoke is greater than in the primary smoke[1]; when ten cigarettes are smoked in 1 hour, the level of COHb in the blood of the non-smoker rises to about the same concentration as that following the active smoking of one cigarette[2]; the amount of urinary nicotine of a non-smoker increases in parallel to the number of active smokers generating smoke, demonstrating a dose response effect[3];benzpyrene in the urine of a non-smoker exposed to smoke becomes detectable, and this amount decreases when the non-smoker avoids exposure to smoke[4]; upon exposure to smoking for 6 hours, the amount of mutagens in the urine of a non-smoker increases markedly[5]; and that mice and dogs exposed to smoke develop lung tumors[6]. These results suggest the possibility of lung carcinogenesis through passive smoking.

Quantitative assessment of passive smoking has been presented in the following findings: The increase in incidence of lung cancer in non-smoking wives of heavy cigarette smokers over that in non-smoking wives of non-smokers was x2.08 in Japan (Hirayama)[7], x3.4 in Greece (Trichopoulos)[9], x3.11 in the United States (Correa)[10], x1.94, also in the United States (Miller)[11], x12.78 in Kanagawa Prefecture (Inoue)[22] and x1.5-2.1 in Hiroshima and Nagasaki (Akiba)[23]. When the findings by Garfinkel (U.S.)[8] and Koo (Hong Kong)[17] are excluded, mortality of non-smoking wives from lung cancer seems to increase about two-fold. Increase in the risk of passive smoking in the family is especially marked in non-smoking women under 50 years of age, while habitual smokers are subject to both active and passive smoking[12]. Akiba[23] found that of women who are not exposed to either active or passive smoking, 100% develop either adenocarcinoma or large cell carcinoma; that the incidence of these tumors decreases to 84% in passive smokers and to 42% in active smokers; and that in the latter cases there is a proportional increase in squamous cell carcinoma and small cell carcinoma [23]. These are similar to our findings.

In these reports, however, there are no consistent results concerning significance or dose response, and there is no unified interpretation at this time.

Some of the explanations for the inconsistencies are the following: (1) Differences in the living environment, (2) lack of definite information on passive smoking before marriage, (3) differences between women who work outside and those who are self-employed, (4) duration of periods when husband and wife are together, (5) smoking habit of the husband and conditions in the home, (7) mealtime habits, (8) incidence of cancer in the family and (9) age when the cancer developed. The paucity of information on these matters has been pointed out[6,13]. The present study was a survey of the Nara region where most women who were the subjects of the investigation were self-employed. Information was gathered regarding the histologic type of tumor, time of exposure to smoking, and incidence of cancer in the family, and although the number of cases was small, a certain degree of control was exercised. Correa[10] studied the relation of lung cancer to past exposure to passive smoking, and concluded that the effect of smoking by the mother could be seen in male lung cancer patients but not in women lung cancer cases.

Extrinsic and intrinsic factors may interact in carcinogenesis. The leading extrinsic factor in lung cancer is presumably cigarette smoking, while genetic cancer may be an intrinsic factor. We investigated the history of relatives three times removed from the principal, and found that with adenocarcinoma there was a strong indication of association of familial incidence of cancer, while with squamous cell carcinoma and small cell carcinoma, association of familial incidence was seen but not to a significant degree in comparison with controls. The association, however, was observed in 4 out of 5 cases of small cell carcinoma while in squamous cell carcinoma there was more variability. There is need for further study in larger numbers of cases. In another investigation of familial factor, the risk of development of lung cancer when there has been a family incidence was 8-fold over cases without any familial occurrence of lung cancer in Kawasaki City, and 5.9-fold in Tokyo[18]. Aoki[19] also pointed out that the risk of cancer of many organs was 2-3 times higher in families which had cases of cancer than in families without such history.

Tokuhata[21], in a survey of 270 cases of lung cancer, assessed the risk when familial incidence and active smoking were combined, and found the following: Compared with individuals without either factor, the risk for the non-smoker with familial history was 3.96-fold; for the smoker without familial history it was 5.45-fold; and for the smoker with familial history it was 13.64-fold. He stated that when corrected for smoking habit, the risk for those with familial history was increased 2.5-fold, approximately the same level of risk as that of smoking and claimed that the two factors are synergistic.

In our present study, the findings indicated that compared with controls,

passive smoking, current or past, increased the risk for lung cancer when familial history was present. When the data were sorted according to histologic type of lung cancer, risk was increased for squamous cell carcinoma and small cell carcinoma when active or passive smoking was combined with familial history, while with adenocarcinoma the influence of familial history was considerable, and the effect of passive smoking in the past was suspected.

Since the number of cases was small and the amount of passive smoking could not be determined so that dose response could not be demonstrated, no definite conclusion could be drawn from the present study, but there was a suggestion that for women in the Nara region, passive smoking is associated with development of lung cancer in women. The effect of passive smoking which has continued to the present time was especially marked, particularly notable in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, the effect of passive smoking in the past was suspected.

Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, was apparent.

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PASSIVE SMOKING IS A RISK FACTOR FOR LUNG CANCER IN NEVER SMOKING WOMEN IN HONG KONG

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INTRODUCTION

In Hong Kong, lung cancer is the leading cause of death due to malignant neoplasms in both sexes. On a world scale, lung cancer death rates among men are not particularly high in Hong Kong. However, the rates in women are among the highest in the world. Four case control studies have been carried out in Hong Kong to investigate the risk factors for lung cancer in women, particularly smoking and passive smoking. They are reviewed as follows:

I. 1976-1977 STUDY

The first major study on risk factors for lung cancer was a case control study on 208 male and 189 female patients. The controls were 204 male and 189 female hospital orthopaedic patients. Smoking was found to be a major risk factor in males with a relative risk (RR) of 27.51. In females, the RR for smoking was only 3.48. 44.4% of the cases were non-smokers whose tumours were predominantly adenocarcinomas (45.2%).[1]

The role of passive smoking was studied by simply asking the question of "Are you exposed to the tobacco smoke of others at home or at work?" For non-smoking women, 40.5% of the cases and 47.5% of the controls had passive smoking. The RR for passive smoking was 0.75 (P=0.38).[2]

II. 1981-1983 STUDY

In the second case control study, 200 female cases and 200 district female controls matched for age were interviewed in depth using a semi-structured questionnaire. The RR for ever smoking was 2.77. 44.0% of the cases had never smoked.

Among the never-smoked wives, 61.4% of the cases and 51.8% of the controls had smoking husband. The RR for passive smoking due to smoking husband was 1.48 (P=0.16).[3]

III. 1981-1984 STUDY

The third case control study included 163 female cases and 185 female controls from hospital orthopaedic patients. Unlike the previous two studies, only histologically and/or cytologically confirmed cases were included. A standardized questionnaire was used for interviewing. The RR for smoking was 4.12. The proportion of cases who were non-smokers was 46.0%.

The role of passive smoking was studied only on the adenocarcinoma cases. For non-smoking women, 61.7% of the adenocarcinoma cases and

44.4% of the controls had passive smoking due to smoking husband. The RR for passive smoking was 2.01 ($P<0.05$). Analysis was also carried out by the site of the tumour. For centrally sited tumour, the RR for passive smoking was 1.61 ($P>0.05$). For peripheral tumour, the RR was 2.64 ($P<0.05$).[4]

IV. 1983-1986 STUDY

This was the largest case control study on lung cancer in women in Hong Kong. A standardized structured questionnaire was designed for interviewing. All the cases were confirmed pathologically. They were compared with 445 female healthy neighbourhood controls matched for age. The RR of ever smoking was 3.81.

45.5% of the cases were never smokers. For never smoking women, 57.8% of the cases and 45.4% of the controls had passive smoking due to a smoking husband. The RR for passive smoking was 1.65 ($P<0.01$, 95% C.I.=1.16, 2.35).

When broken down by cell type, the proportion of never smokers of 62.4% was the highest in adenocarcinoma and it was only in this cell type that the RR for passive smoking was statistically significant (RR=1.87, $P<0.01$, 95% C.I.=1.23, 2.85). Significant trends for RR with amount smoked daily by husband were observed for all cell types combined and for adenocarcinoma only.

TABLE I
SUMMARY OF RESULTS ON PASSIVE SMOKING AMONG NON-SMOKING WOMEN IN 4 CASE CONTROL STUDIES IN HONG KONG

Study*	Cases/Controls		Total no. of cases & controls	Relative risk	P value
	Passive smoking	No passive smoking			
1976-1977 Chan & Fung, 1983	34/66	50/73	223	0.75	0.38
1981-1983 Koo et al, 1985	54/71	34/66	225	1.48	0.16
1981-1984 Lam WK, 1985	37/64	23/80	204	2.01	0.03
1983-1986 Lam TH et al, 1987	115/152	84/183	534	1.65	0.007
Grand Total	240/353	191/402	1,186	1.43**	0.004

* The study by Lam WK included only adenocarcinoma whereas the other three studies included all cell types.

** Summary relative risk by Mantel Haenszel's method

SUMMARY OF RESULTS ON PASSIVE SMOKING

Table I shows the summary of results of the above four studies. Apart from the earliest study in which only one simple question was asked about passive smoking, they all showed a RR greater than unity. Statistical significance was reached in the recent two. **The Mantel-Haenszel's summary RR was 1.43 ($P<0.01$, 95% C.I.=1.12, 1.83).**

In a review of epidemiological and other evidence on passive smoking and lung cancer, Blot and Fraumeni estimated a 30% excess risk[6] while Wald et al calculated a relative risk of 1.35 by pooling the results of ten case control studies and three prospective studies.[7] The summary RR of the four case control studies in Hong Kong is close to these estimates. Because the local prevalence of smoking among women was low (4.1%),[8] the influence by misclassification bias would be much less than in western countries and could not account for the relatively high RR. **The results in Hong Kong therefore strongly suggest that passive smoking is a risk factor for lung cancer in never smoking Chinese women.**

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Epidemiologic Characteristics and Multiple Risk Factors of Lung Cancer in Taiwan*

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Abstract. *The specific aim of this study was to examine epidemiologic characteristics and multiple risk factors of lung cancer in Taiwan. The age-adjusted mortality from lung cancer has been increasing since the early 1950s with a constant male-to-female ratio of around 2.0. International comparison of cumulative moratlity from lung cancer showed a much lower male-to-female ratio in Chinese than in other populations. Significantly high moratlity from lung cancer was observed in highly urbanized cities and the endemic area of chronic arsenicism in Taiwan. Significant associations of active and passive cigarette smoking with epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung were observed in a hospital - based case - control study carried out in Taipei metropolitan areas. Alcohol drinking, coffee drinking and various types of indoor air pollution were not related to lung cancer after the cigarette smoking habit was adjusted through a multiple logistic regression analysis.*

Lung cancer is one of the most important cancers in Taiwan where malignant neoplasm has become the leading cause of death since 1982. The mortality from lung cancer ranked the second in both men and women among various cancer sites in Taiwan (1). The annual number of deaths from lung cancer was as high as 2,500-3,000 in the 1980s (2). It has resulted in a significant socioeconomic impact with a work-year loss of 12,500 annually (1).

The one-year survival rate of lung cancer patients was reported as less than 20% in Taiwan (3). The early detection of lung cancer by chest X-ray, sputum cytology and / or fiber optic bronchoscopy remains ineffective and inefficient (3-5). Other screening methods, including tumor marker levels, still need further evaluation (6). Primary prevention and intervention become an important task in the control of the disease. The identification of risk factors for lung cancer is essential for an effective and efficient primary prevention.

Both genetic and environmental risk factors have been related to the development of lung cancer. Risk factors which have been documented include active and passive cigarette smoking, occupational and environmental exposures to arsenic, asbestos, chromium, mustard gas, radon and polyaromatic hydrocarbons, as well as inadequate consumption of dark green vegetables (7-11). Populations in different areas may have different risk factors for lung cancer, and the same risk factors may be of different importance in different populations and / or areas. The study of risk factors in various populations is important not only for the disease control program, but also for the elucidation of its etiological mechanism.

Although epidemiologic characteristics of lung cancer in Taiwan have been described in two previous reports (12, 13), there has never been a case-control study aimed at elucidating possible risk factors for lung cancer in Taiwan. In this report, we updated the analysis of epidemiologic characteristics of lung cancer mortality and incidence, and examined multiple risk factors for the disease based on a hospital - based matched case - control study.

Materials and Methods

Analysis of mortality and incidence rates. The data on lung cancer deaths

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Table I: *Secular trend of age-adjusted lung cancer mortality rates per 100,000 population from 1954 to 1988 in Taiwan by sex.*

Year	Age-adjusted mortality		Male-to-female
	Male	Female	ratio
1954-1958	3.88	2.07	1.87
1959-1963	6.49	3.53	1.84
1964-1968	10.35	5.84	1.77
1969-1973	13.97	6.68	2.09
1974-1978	16.65	8.29	2.01
1979-1983	21.79	10.42	2.09
1984-1988	24.91	12.22	2.04

from 1954 to 1988 were obtained from the Taiwan Provincial Department of Health which is in charge of the death certification system in Taiwan. Population data for the same period were abstracted from annual demographic statistics (14). As it is mandatory to register any event of birth, death, marriage, employment and education in household registration offices, mortality data are quite complete and accurate in Taiwan. The incidence of lung cancer in Taiwan was derived from annual reports of national cancer registry (15). As the completeness and accuracy of cancre registry has been assessed in Taipei City only, the incidence data analyzed in this report were limited to those of Taipei City. The mortality from lung cancer in 17 selected countries was obtained from the annual vital statistics published by the World Health Organization (16). Incidence rates of lung cancer among Chinese males and females in San Francisco, Los Angeles, Hawaii, Hong Kong and Shanghai were abstracted from the registration data published by the International Agency for Research on Cancer (17).

In the analysis of mortality and incidence, age-sex-specific rates were first calculated for different areas and / or calendar years. The age was stratified into 15 five-year groups from less than 5 to 70 or more. Age-adjusted mortality and incidence rates were calculated using world population in 1976 (17) as the standard population for the study of secular trend, migrant comparison and geographical variation in Taiwan, while cumulative mortality rates over the age range from 0 to 84 years were for international comparison.

Hospital-based matched case-control study. As most patients suspected of having lung cancer are referred to teaching hospitals for confirmatory diagnosis and treatment in Taiwan, we recruited serial patients with lung cancer from four major teaching hospitals in Taipei City. All patients were newly diagnosed and pathologically confirmed. A total of 354 new cases were recruited and 332 (93.8%) agreed to participate in the study. Hospital controls group-matched with case on hospital, age and sex were recruited from ophthalmic patients of study hospitals with a control-to-case ratio of 3:1. Among 664 recruited controls, 635 (95.6%) of them agreed to participate in the study.

A structured questionnaire was used to obtain socio-demographic characteristics and the history of exposure to risk factors including cigarette smoking, alcohol drinking, tea and coffee drinking, as well as indoor air pollution resulting from burning incense and mosquito coils. The consumption frequency, quantity and duration were inquired for habits of cigarette smoking, alcohol drinking, tea drinking and coffee drinking.

In addition to the questions mentioned above, the interview time and interviewer - assessed reliability of the interviewee's response were also included. The average interview time in minutes was 37.4 and 31.5 respectively for cases and hospital controls. There were 9 (2.7%) cases and 18 (2.8%) controls whose responses were rated as unreliable because of poor memory and / or cooperation. In all, there were 323 cases and 617 hospital controls available for the final analysis. With regard to the pathological type of the 323 lung cancer patients, there were 133 (41.2%) affected with epidermoid carcinoma, 47 (14.6%) with small cell carcinoma, 134 (41.5%) with adenocarcinoma, and 9 (2.8%) with other minor pathological types.

In the univariate analysis, the odds ratio and its statistical significance of each risk factor were assessed for three major pathological types of lung cancer. Mantel - Haenszel chiquare test (18) was used to assess the statistical significance of age-sex-adjusted odds ratios for each risk factor. As several risk factors were inter-correlated, multiple logistic regression analysis (19) was used to estimate multivariate - adjusted odds ratios. In the regression analysis, only significant risk factors observed in the univariate analysis were included in the regression equation. BMDP statistical software was used to estimate regression coefficients through the maximum likelihood method (19).

Results

Secular trend. The secular trend of lung cancer mortality from 1954 to 1988 in Taiwan is shown in Table I. The age - adjusted mortality rate of lung cancer increased strikingly during the period for both males and females; it increased significantly from 3.88 per 100,000 in 1954-1958 to 24.91 per 100,000 in 1984-1988 for males, and from 2.07 per 100,000 in 1954-1958 to 12.22 per 100,000 in 1984-1988 for females. The male-to-female ratio of age-adjusted lung cancer mortality remained around 2.0 during the period from 1954 to 1988.

International comparison, migrant difference and geographical variation. The international comparison of lung cancer mortality in Taiwan and 17 selected countries is shown in Table II. Males in Scotland and The Netherlands had the highest mortality from lung cancer, while males in Taiwan and mainland China had the lowest. Females in Hong Kong and Scotland had the highest mortality, while females in the Netherlands and mainland China had the lowest. The cumulative mortality rate of lung cancer in Taiwan ranked as the 17th and 9th, respectively, for males and females. The male-to-female ratio of the cumulative mortality rate of lung cancer varied significantly from greater than 6.0 in the Netherlands, West Germany and Italy to less than 3.0 in Taiwan, China and Hong Kong.

The comparison of age-adjusted incidence rate of lung cancer among Chinese in different areas is shown in Table III. The rate for males was highest in Singapore and lowest in Taipei, while that for females was highest in San Francisco and lowest in Los Angeles. The male-to-female ratio in age-adjusted mortality from lung cancer ranged from 1.33 in Hawaii to 3.43 in Singapore.

There was also a striking geographical variation of lung cancer mortality among 361 townships and precincts in Taiwan. Generally speaking, males and females had similar geographical variation in age-adjusted mortality of lung cancer with a correlation coefficient of 0.54. High lung cancer mortality was observed in highly urbanized cities as well as in the endemic area of chronic arsenicism, while low mortality was observed in rural townships where aboriginals and Hakka Taiwanese reside. There was a significant correlation in the geographical variations of lung cancer with cancers of the liver, pancreas, bladder and kidney in males and females as

Table II. *Comparison of cumulative mortality from lung cancer in Taiwan and 17 selected countries.*

Rank	Male		Female	
	Country	CMR	Country	CMR
1	Scotland	21.22	Hong Kong	5.95
2	Netherlands	20.04	Scotland	4.40
3	England & Wales	18.61	Singapore	4.37
4	Hong Kong	13.97	England & Wales	3.97
5	Singapore	13.87	USA	3.43
6	Hungary	13.82	Ireland	3.24
7	Austria	13.52	Canada	2.79
8	Canada	13.16	Hungary	2.56
9	USA	13.04	Taiwan	2.52
10	West Germany	12.99	Israel	2.39
11	Australia	12.59	Australia	2.07
12	Italy	11.47	Japan	2.06
13	Ireland	11.05	Austria	2.05
14	Japan	7.38	West Germany	1.56
15	Israel	7.14	Italy	1.48
16	Chile	5.08	Chile	1.45
17	Taiwan	4.98	Netherlands	1.43
18	China	1.95	China	0.93

CMR: Cumulative mortality rates, 0-84 years (percent)

Table III. *Age-adjusted incidence rates per 100,000 population of lung cancer among Chinese in six cities in Asia and USA.*

City	Age-adjusted mortality		Male-to-female
	Male	Female	ratio
Singapore	68.0	19.8	3.43
San Francisco	57.8	25.1	2.30
Hong Kong	55.5	23.4	2.37
Shanghai	51.2	18.1	2.83
Los Angeles	33.8	13.6	2.49
Hawaii	31.4	23.6	1.33
Taipei	27.7	14.4	1.92

Table IV. *Ecological correlation between age-adjusted mortality rates of lung cancer and other cancers in 361 townkships and precincts in Taiwan.*

Correlation	Male	Female
Lung *vs.* liver	0.17	0.24
Lung *vs.* pancreas	0.29	0.21
Lung *vs.* bladder	0.35	0.74
Lung *vs.* kidney	0.24	0.66
Lung *vs.* prostate	0.29	-

well as with cancer of the prostate in males, as indicated in Table IV.

Case-control study. Table V shows frequency distributions of age and sex of 133 epidermoid carcinoma, 47 small cell carcinoma and 134 adenocarcinoma patients and of 617 ophthalmic hospital controls. They were all comparable in the distribution of age and sex. The age-sex-adjusted odds ratios for cigarette smoking on the development of various pathological types of lung cancer are shown in Table VI. There was a significant association between cigarette smoking and epidermoid carcinoma, small cell carcinoma and adeno-carcinoma of the lung, with an odds ratio of 6.66, 3.59 and 2.08, respectively. Futhermore, the duration, quantity and inhalation degree of cigarette smoking were all significantly associated with three pathological types of lung cancer in a dose-response relation. Passive smoking was also correlated with the development of epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung with a significant odds ratio of 4.68, 2.55 and 3.04, respectively.

The age-sex-adjusted risk of developing various pathological types of lung cancer for alcohol drinking, tea drinking and coffee drinking are shown in Table VII. Alcohol drinking was significantly associated with epidermoid carcinoma of the lung with an odds ratio of 1.57. Neither small cel carcinoma nor adenocarcinoma was significantly correlated with alcohol drinking. None of the habits of drinking black tea, half-processed tea and green tea was significantly associated with any pathological type of lung cancer. Coffee drinking was found to be associated significantly with epidermoid carcinoma of the lung only.

Table VIII shows associations between various kinds of indoor air pollution and pathological types of lung cancer. Neither burning incense at home nor type of cooking fuels was related to the development of any type of lung cancer. Burning mosquito coils at home was found to be significantly associated with the development of epidermoid carcinoma and adenocarcinoma of the lung, with an odds ratio of 1.81 and 1.70, respectively.

As risk factors significantly associated with various pathological types of lung cancer were inter-correlated, a multiple logistic regression analysis was empolyed to assess multivariate - adjusted odds ratio for various variables. Separate regression analysis was carried out for each pathological type of lung cancer. Only active and passive cigarette smoking were significantly associated with the three pathological types of lung cancer. Alcohol drinking, coffee drinking and burning mosquito coils at home were not significantly associated with any pathological type of lung cancer after cigarette smoking was adjusted.

Discussion

Increasing secular trend and significant geographical variation are two interesting epidemiologic characteristics of lung cancer. This suggests the importance of environmental factors in the determination of the disease. In this study, we observed an increase in lung cancer mortality in Taiwan since the early 1950s. The result is consistent with those observed in most countries (20). The increas in age-adjusted lung cancer mortality in Taiwan may be attributable to improved diagnostic methods, increased consumption of cigarettes,

Table V. *Age and sex distributions of 133 epidermoid carcinoma, 47 small cell carcinoma, and 134 adnocarcinoma patients and 617 opthalmic hospital controls in metropolitan Taipei areas.*

Variable	Group	Epidermoid carcinoma No. (%)	Small cell carcinoma No. (%)	Adeno-carcinoma No. (%)	Hospital controls No. (%)
Age	< 55	21 (15.8)	17 (36.2)	38 (28.4)	146 (23.7)
	55-64	59 (44.4)	14 (29.8)	50 (37.3)	244 (39.5)
	65 +	53 (39.8)	16 (34.0)	46 (34.3)	227 (36.8)
Sex	Male	111 (83.5)	36 (76.6)	101 (75.4)	488 (79.1)
	Female	22 (16.5)	11 (23.4)	33 (23.4)	129 (20.9)

Table VI. *Age-sex-adjusted odds ratios for cigarette smoking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Habit	Yes	6.66***	3.59***	2.08***
	No	1.00	1.00	1.00
Duration (year)	41+	8.43***	5.12***	3.79***
	31-40	6.52	4.30	1.60
	21-30	2.76	3.33	1.52
	1-20	1.70	2.16	1.23
	None	1.00	1.00	1.00
Quantity (cig./day)	31+	11.11***	8.09***	3.61***
	21-30	7.61	4.64	2.34
	11-20	7.05	3.48	1.74
	1-10	2.59	2.45	1.21
	None	1.00	1.00	1.00
Inhalation	Deep	7.23***	4.37**	2.21*
	Shallow	3.67	3.57	1.92
	None	1.00	1.00	1.00
Passive smoking	**Yes**	**4.68***	**2.55***	**3.04***
	No	**1.00**	**1.00**	**1.00**

* p < 0.05. **p < 0.01. *** < 0.001 based on Mantel - Haenszel chi-square tests.

Table VII. *Age-sex-adjusted odds ratios for beverage drinking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Alcohol drinking				
Habit	Yes	1.57*	1.36	1.17
	No	1.00	1.00	1.00
Frequency (days/week)	4+	1.72*	1.90	1.50
	1-3	1.43	0.90	0.98
	None	1.00	1.00	1.00
Tea drinking				
Black tea	Yes	0.20	1.10	0.19
	No	1.00	1.00	1.00
Half-processed tea	Yes	1.52	0.99	0.99
	No	1.00	1.00	1.00
Green tea	Yes	1.48	1.20	1.77
	No	1.00	1.00	1.00
Coffee drinking	Yes	2.10*	1.44	1.25
	No	1.00	1.00	1.00

* P < 0.05 based on Mantel - Haenszel chi-square tests

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Table VIII. *Age-sex-adjusted odds ratios for various types of indoor air pollution on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Burning incense	Yes	0.77	1.33	0.99
	No	1.00	1.00	1.00
Burning mosquito coils	Yes	1.81*	1.13	1.70*
	No	1.00	1.00	1.00
Cooking fuels	Wood & coal	0.85	1.08	1.02
	Charcoal, gas & electricity	1.00	1.00	1.00

* $p < 0.05$ based on Mantel - Haenszel chi - square tests.

rapid industrialization and urbanization, and worsened air pollution. International comparison of cumulative mortality from lung cancer revealed a striking difference in the male-to-female ratio among 18 countries studies. The reason for a much lower male-to-female ratio among Chinese in various countries deserves further investigation. As most Chinese women are non-smokers and 60% of female lung cancer patients are affected with adenocarcinoma (12), it seems reasonable to suspect that risk factors other than active cigarette smoking are involved in the development of adnocarcinoma. The striking geographical variation in lung cancer mortality among 361 townships and precincts in Taiwan also suggests the importance of environmental factors. Heavy air pollution resulting from urbanization and industrialization may at least partly contribute to the high mortality from lung cancer in cities. Consumption of high-arsenic artesian well water has been documented to be the major risk factor for lung cancer in the endemic area of chronic arsenicism (21). The significant ecological correlation between mortality rates of lung cancer and pancreas cancer may be explained by the better dignosis of the latter in urbanized areas. However, the similar geographical variation in mortality from cancers of the lung, liver, bladder, kidney and prostate may be attributable to their associations with arsenic exposure from drinking water.

In our case-control study, both active and passive cigarette smoking were significantly associated with the development of three pathological types of lung cancer. Almost all epidemiological studies and animal experiments consistently show a significant association between cigarette smoking and lung cancer (7-9, 22). Both epidermoid carcinoma and small cell carcinoma had a stronger association with active cigarette smoking than adenocarcinoma in this study. This observation is consistent with those reported previously. However, there was no difference in the association with passive cigarette smoking for the three pathological types of lung cancer. Futher investigations are needed to explain such a discrepancy.

Habits of alcohol drinking and coffee drinking were significantly associated with the development of epidermoid carcinoma of the lung in the univariate analysis in this study. However, the association was no longer significant after further adjustment for the effect of cigarette smoking. Indoor air pollution has been documented to cause lung cancer in Yunnan Province of China (10). In this study, an effort was made to assess the effects of various types of indoor air pollution on the development of lung cancer. Although a significant association between lung cancer and burning mosquito coils at home was observed in the univariate analysis, it became not significant after active and passive cigarette smoking were adjusted for. The reduction of cigarette smoking through public education remains the most important task for the primary prevention of lung cancer.

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Dr. G. H. Miller, the author of "The Impact of Passive Smoking: Cancer Deaths among Nonsmoking Women" requested that a revised Abstract be printed to clarify several points.

ABSTRACT

In order to obtain an estimate of the impact of passive smoking on cancer mortality, a retrospective study was conducted examining the cancer mortality of nonsmoking wives with no known or minimal exposure in contrast to nonsmoking wives with moderate to life-time exposure to tobacco smoke. The study was based on the data from 906 deceased nonsmoking women who resided in Erie County, Pennsylvania, who were divided into the following three categories:

1. No known exposure
2. Exposed nonemployed
3. Employed (assumed to be exposed to environmental tobacco smoke in the workplace)

The data were analyzed by the retrospective case-control method using cancer deaths as the cases and non-cancer related deaths as the controls. Also, the data from 401 smoking women were used for comparative purposes of the total percentage of cancer deaths among three groups:

1. Nonsmoking, nonexposed women
2. Combined nonsmoking unemployed and employed exposed women
3. Smoking women

The major finding from the study are

1. Only (2.2%) of the total deaths reported among the nonsmoking women with no known or minimal exposure to tobacco smoke were due to cancer of any site.
2. No cases of lung cancer deaths were reported for the nonexposed, nonsmoking women, and eight lung cancer deaths were reported among the nonsmoking women who were exposed to passive smoking. Also, for this small group of 179 nonsmoking nonexposed women, there were no reported cases of breast cancer, genitourinary or lymphatic cancer.
3. Employed nonsmoking women experienced proportionately more cancer deaths (34.3%) than both nonexposed (2.2%) and exposed nonemployed wives (18.9%). The combined groups of exposed nonsmoking wives (nonemployed and employed) contracted 25.5% cancer deaths.
4. Age-adjusted data showed similar trends.
5. Cancer death rates for women smokers was 35.5% of the total deaths of women smokers.

Public health officials should consider requiring that the workplace be free from tobacco smoke since these data imply that passive smoking has a very detrimental effect upon nonsmokers. Also, smokers should be made aware of the potential damage they inflict on others in their home as well as the workplace.

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The Impact of Passive Smoking: Cancer Deaths among Nonsmoking Women

G.H. Miller, Ph.D., CPC

ABSTRACT

In order to obtain an estimate of the impact of passive smoking on cancer mortality, a retrospective study was conducted examining the cancer mortality of nonsmoking wives with no known or minimal exposure in contrast to nonsmoking wives with moderate (up to 19 years) to lifetime exposure to tobacco smoke. The study was based on the data from 906 deceased nonsmoking women from Erie County, Pennsylvania, who were divided into the following three categories:

1. No known exposure
2. Exposed nonemployed wives
3. Employed wives assumed to be exposed to environmental tobacco smoke in the workplace

The data were analyzed by the retrospective case-control method using cancer deaths as the cases and non-cancer related deaths as the controls. The major findings from the study are

1. Only 2.2% of the deaths reported among the women with no known or minimal exposure to tobacco smoke were due to cancer of any site.
2. No cases of lung cancer were reported for the nonexposed women, and eight lung cancer deaths were reported among the nonsmoking women who were exposed to passive smoking.
3. Employed women experienced proportionately more cancer deaths (35.3%) than both nonexposed (2.2%) and exposed nonemployed wives (25.5%).
4. Age-adjusted data showed similar trends.

Public health officials should consider requiring that the workplace be free from tobacco smoke since these data imply that passive smoking has a very detrimental effect upon nonsmokers both at home and in the workplace.

Key Words: passive smoking, lung cancer, breast cancer.

I. INTRODUCTION

Whether or not passive smoking is detrimental to health has been extensively considered in the last decade. The first reports on the effects of long-term exposure to passive smoking appeared in the late 1970s.[1-3] Prior to that time, it was generally assumed that passive smoking was not of much consequence. However, most health professionals were aware of reports of moderate-to-severe eye irritation as well as allergic reactions to tobacco smoke.[1-3] There were also reports of the serious health consequences observed in animals after exposure to high concentrations of tobacco smoke.[1] In the 1970s, research reports discussed the effect of increased respiratory diseases in children of smoking parents.[2] These were followed by the 1980 Surgeon General's report on the harmful effects of cigarettes on the health of smoking women, including research reporting lower birthweights among children of smoking mothers.[4] Passive smoking has been associated with deleterious effects on the fetus.[5,6]

In 1978[7] and 1979,[8] at the Third World Conference on Smoking and Health, Miller[7,8] proposed a passive smoking classification based on three different exposure levels: (1) short-term — a few minutes to a few hours; (2) moderate-term — less than 2 decades; and (3) long-term — 2 decades to a lifetime. He suggested that studying the consequences of long-term exposure provided the best opportunity for observing the effects, if any, of passive smoking. He reported a 4-year earlier average-age-at-death of nonsmoking women exposed to their husbands' cigarette smoke compared with nonsmoking, nonexposed women.

White and Froeb[9] in 1979 reported severe lung dysfunction following long-term exposure to tobacco smoke. Hirayama,[10] Tricopolous et al.,[11] and and Correa et al.[12] noted a two- to threefold increase in lung cancer in exposed wives when compared to nonexposed wives. Gillis et al.[13] and Schmidt et al.[14] have also shown that passive smoking is detrimental to the health of the nonsmoker. Miller,[15] Sandler et al.,[16] and Repace and Lowrey[17] each showed a two- to threefold increase in total cancer deaths following long-term exposure to passive smoking. Garfinkel et al.,[18] who had previously found no statistically significant evidence of the detrimental effects of passive smoking, now reports a two- to threefold increase in lung cancer.[19] Wald et al.[20] and Pershagen et al.[21] most recently have provided support for the hypothesis that passive smoking increases lung cancer incidence, largely among spouses. Two reports provide a detailed review of the research on passive smoking, noting its detrimental effects: the Surgeon General[22] recommended a smoke-free environment, and the National Academy of Sciences[23] recommended no smoking in the home environment of children.

In order to obtain additional information on the effects of passive smoking, this study compared different levels of environmental tobacco smoke exposure of married nonsmoking

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women with cause of death. The causes of death included in the study were the usual causes of death such as cardiovascular, cancer, and respiratory diseases but excluded traumatic deaths such as accidents, suicides, and homicides. Men were not included in this study since so many men are exposed to environmental tobacco smoke in the workplace.

II. MATERIALS AND METHODS

A. The Population

The population of Erie County, which includes Erie, the third largest city in Pennsylvania, was 263,654 in 1970. It is primarily a middle income population (the average family income for 1970 was listed as $9,380) with a low migration rate of 7% for the 1950 to 1970 time period as reported by the Pennsylvania Department of Commerce.

B. Methodology

The Northwestern Pennsylvania Study on Smoking and Health (NPSSH) began to gather data in 1973 on the smoking habits of deceased male and female residents in Erie County by interviewing the decedents' next of kin. Death notices for the years 1972 through 1982 were obtained from the local newspaper, which lists the names of approximately 95% of deceased Erie County residents along with information on surviving relatives.

Telephone numbers of one to three surviving relatives were obtained for approximately 85% of the death notices reported in the newspaper. Deaths from accidents, suicides, congenital anomalies, and persons younger than 30 years of age were not included because an age bias is introduced when those classified in these categories have their lives curtailed and therefore would not provide an accurate estimate of the age at which cancer actually occurs for the passive smoking-exposed women. Because of the reduced life expectancy, the inclusion of accidents and suicides would lower the incidence of cancer since those in the lower age cohorts might have contracted some type of cancer had they lived long enough. These individuals comprised about 10% of the total deaths.

A questionnaire designed for telephone interviews was constructed with the assistance of the local branches of the American Cancer Society, the American Heart Association, the American Lung Association, and by smoking and health experts in the Pennsylvania Department of Health. A more detailed description of this questionnaire has been published.[15]

Interviewers explained the purpose of the study to the identified surviving relatives and solicited their cooperation. Information was collected from them on each decedent's cause of death, age, occupation (including information on whether or not the wife worked outside the home), exposure to known sources of pollution (including environmental tobacco smoke), smoking history, and whether or not the spouse and parents smoked. The interviews were conducted by the director of the study and by interviewers trained by him.

The questionnaire was revised in 1975, and additional items were included to obtain more complete information on a spouse's smoking habits such as type and quantity of tobacco used, details on smoking cessation, the age at the time of death and the cause of death, the current age if living, the year or decade of death if deceased. Information on whether any other members of the household smoked was also added.

Detailed data on passive smoking from the revised questionnaire were gathered on the decreased from 23 months in the years 1975, 1976, 1979, and 1980; these were the only data considered in this study. Due to logistical problems, the interviews for deaths occurring in other months were not completed at that time. The total number of deaths among residents of Erie County for these 4 years (Pennsylvania Department of Health) was 10,131 (5478 men and 4653 women). Among the 3538 relatives contacted, 3361 (95%) provided information on 1863 men and 1498 women. Of the 1498 deceased women for whom information was obtained, smoking exposure histories were available for 1423 — 906 nonsmoking wives, who are the subjects considered in this paper, plus data on 401 smokers. Of the remaining 116 deceased nonsmoking women, 63 never married and 53 did not have sufficient information on passive smoking to include in this study. For example, the statement that a husband was a smoker was not considered sufficient evidence if details on amount and type of tobacco use were unavailable, resulting in the exclusion of the wife from this study. These data are summarized in Table I.

In this study, a nonsmoker was defined as a person who had smoked fewer than 20 packs of cigarettes during his or her lifetime. A nonsmoking, nonexposed wife was one who had no known reported exposure to tobacco smoke from any source or minimal exposure (only occasional exposure to pipe, cigar, or cigarette smoke). A nonemployed exposed wife was one who was exposed to cigarette smoke by a family member

Table I
Total Deaths from All Causes, Total Cancer Deaths, and Number of Interviews from the Erie County Population Data Base for the Years 1975, 1976, 1979, and 1980

	All causes	All cancer	Total interviews	Interviews passive smoking	Interviews used in study
Men	5,478	1,116	1,863	1,793	
Women	4,653	995	1,498	1,423	906*
Total	10,131	2,111	3,361	3,216	

* This figure includes only nonsmoking women with detailed information on passive smoking exposure. It excludes 401 smoking wives and 116 who were never married, single, or of uncertain passive smoking status.

(husband, children, or relatives) or a nonfamily member, or had reported long-term exposure to smoky rooms in non-employed activities outside the home. An employed wife was identified by a surviving relative as a person engaged in an occupation outside the home for more than 3 years.

In order to insure a clearly defined category for nonexposure, all those who may have had any potential moderate-to-heavy exposure were eliminated from this category. Therefore, those not included in the nonexposed spouse category, in addition to the 401 smoking women, were (1) women who were married at any time to a smoker; (2) women exposed by family or friends or exposed in nonemployed activities; (3) all non-smoking employed women.

Although some nonexposed individuals might have been eliminated by these definitions, the nonexposed category as defined here is as free as possible from the inclusion of those who may have been exposed for longer periods of time. The nonsmoking wives were categorized in the following three groups based upon the information reported in the telephone interviews with relatives:

1. NX — nonexposed (no known or only minimally exposed) wives
2. ENE — exposed nonemployed wives
3. EW — Employed wives who were assumed to have some exposure at work

The data were analyzed using the retrospective case control techniques described by Fleiss.[24] The "cases" were defined as deaths (among nonsmoking wives) due to cancer of any kind while the "controls" were noncancer deaths among nonsmoking wives. These deaths included cardiovascular, respiratory, kidney, and other noncancer diseases, but excluded traumatic deaths such as accidents and suicides.

The classification of the cause of death as recorded on the death certificate was provided by the ICD (International Classification of Diseases) codes listed on computer printouts provided by the Pennsylvania Department of Health. The causes of death reported by the next of kin were not used since the ICD codes are considered more accurate. However, the information provided by the surviving relatives was very close to the ICD codes when comparison was made between the next of kin's report of the cause of death given during the interview and the ICD (Death Certificate) disease designation. Details on these data will be reported separately.

In order to be sure that all those classified as having no known exposure to carcinogenic compounds of tobacco smoke were classified correctly, very close relatives of the deceased were located and interviewed if the first interviewee was not a close relative, or close relatives were interviewed again to obtain greater accuracy in the classification of the nonexposed. During this interviewing, it was discovered that two women classified as nonexposed who died of breast cancer were actually exposed to cigarette smoke by their husbands and children. This reduced the total cases of cancer among nonexposed women from six to four.

Because of the small numbers with different types of cancer, only the major cancer categories were considered as noted in the standard International Classification of Diseases: Oral (140–149), Digestive tract (150–159), Respiratory (160–163), Breast (174), Genitourinary (180–189), Lymphatic (200–209), and All Other Cancer Sites.

Although specific details on cancer deaths due to smoking are not considered in the present study, a comparison was made with the nonexposed (NX), the exposed nonsmokers (ENE and EW), and smokers (employed and nonemployed) to provide comparisons between the nonexposed, exposed nonsmokers, and smokers.

In order to check for potential bias due to age, the data were age adjusted for all cancer causes and for the major categories of cancer: oral, breast, lung, respiratory, genitourinary, and lymphatic.

III. RESULTS

Analysis of the data in the two by three contingency table [(Table II—two categories: cancer cases and noncancer cases compared with the three categories: NX (nonexposed wives), ENE (exposed nonemployed wives), EW (employed wives)]

Table II
Deaths among Nonexposed and Exposed Nonsmoking Wives

	Cancer deaths	Noncancer deaths	Total deaths	Percent cancer deaths
Nonexposed,				
(1) nonemployed	4	175	179	2.2
Exposed,				
(2) nonemployed	78	334	412	18.9
(3) Employed	108	207	315	34.3
Total	190	716	906	21.0

Chi square for above 3 by 2 matrix (2 DF) = 72.64

Chi square evaluations for 2 by 2 comparisons (1 DF)

		Odds ratio	Chi square
(1) vs. (2)	(Nonexposed vs exposed nonemployed wives)	10.2	29.0
(1) vs. (3)	(Nonexposed vs. employed wives)	22.8	66.9
(2) vs. (3)	(Exposed nonemployed wives vs employed wives)	2.2	22.3
(1) vs [(2) + (3)]	(Nonexposed vs. exposed nonemployed and employed wives)	15.0	47.2

showed a Chi Square value of 72.64 with 2 degrees of freedom ($p \leq 0.01$).

Table II also shows four different comparisons of the three subgroups: (1) nonexposed wives (NX) with exposed nonemployed wives (ENE); (2) nonexposed wives (NX) with employed wives (EW); (3) exposed nonemployed wives (ENE) with employed wives (EW); and (4) nonexposed wives (NX) compared with the combination of exposed nonemployed wives (ENE) and employed wives (EW). The data from Table II show that exposure to environmental tobacco smoke is associated with increased cancer mortality resulting in an odds ratio of 10.2 when comparing nonexposed wives with nonemployed wives; an odds ratio of 22.8 when comparing nonexposed wives with employed wives; an odds ratio of 2.2 when comparing exposed nonemployed wives with employed wives; and an odds ratio of 15.0 when comparing nonexposed wives with exposed nonemployed wives and employed wives.

Proportionally far fewer nonsmoking nonexposed wives died of cancer than the exposed wives. The comparison of the exposed nonemployed wives with employed wives also showed highly significant excesses in cancer mortality among the employed women.

Table III shows the mortality from cancer by primary site for the three different exposure groups (NX — nonexposed wives; ENE — exposed nonemployed wives, and EW — employed wives) for the major categories of cancer (oral, digestive tract, breast, genitourinary, lymphatic, and other sites). There were no reported deaths from oral, lung, breast, genitourinary, and lymphatic cancer among the 179 deaths within the nonexposed women. One death from digestive cancer and three deaths from "other" cancers were reported for the nonexposed. Eight deaths due to lung cancer were reported among the 727 deaths of exposed (nonemployed and employed) nonsmoking wives.

Figure 1 shows the percentage of deaths due to cancer among nonexposed wives, exposed wives (both nonemployed and employed), and smoking wives. Although smoking wives are not considered in detail in the present study, the preliminary data are provided here for comparative purposes:

1. Nonexposed nonemployed wives — 2.2%
2. Exposed (employed and nonemployed) wives — 25.5%
3. Smoking wives (employed and nonemployed) — 35.3%

In addition, the data for cancer deaths were age adjusted by the standard age-adjusting methods. The cancer deaths were adjusted to cause distribution of all female decedents in the years considered in this study (1975, 1976, 1979, 1980) from Erie County based on the data from the Pennsylvania Department of Vital Statistics. The results of the expected and observed were analyzed by the two-way probability based on the Poisson distribution and are reported in Table IV. The Poisson distribution was used since the nonexposed group had so few cases. Table IV shows the results after age adjusting for all cancer cases, digestive cancer, and the results for the combination of oral, lung, breast, genitourinary, and lymphatic cancers which appear to be associated with effects of passive smoking.

IV. DISCUSSION

While many epidemiologists prefer to conduct prospective studies, the retrospective study has the advantage of allowing one to obtain estimates in a short time. Thus, this type of a research provides mortality data related to information on the smoking habits of the deceased.

Because nonsmoking women may be exposed to numerous sources of tobacco smoke, this study tried to eliminate as many of the sources of tobacco smoke exposure as possible in order to more accurately classify women into a "pure" nonexposed category. It is probable that persons in this "pure" category have had some small exposures to tobacco smoke during their lives, because minimal exposure is difficult to avoid.

The present study was designed to obtain smoking history data on all nonsmoking wives who died during the specified years. While it is difficult, if not impossible, to obtain data on all members of a population, there is little reason to believe that the 23-months' sampling of the 4-year population was

Table III
Major Types of Cancer for Nonexposed and Exposed Nonsmoking Wives

Type of cancer	Oral	Digestive tract	Respiratory	Breast	Genitourinary	Lymphatic	Other sites	Total	Average age at death
ICD classification	140—149	150—159	160—163	174	179—185	200—209			
NX	0	1	0	0	0	0	3	4	84.5
ENE	0	28	3	14	9	8	16	78	71.1
EW	0	38	5	25	14	10	16	108	67.8
Total	0	67	8	39	23	18	35	190	

Note: ICD: International classification of disease; NX: nonexposed wives; ENE: exposed nonemployed wives; EW: employed wives; Total: exposed and nonexposed wives.

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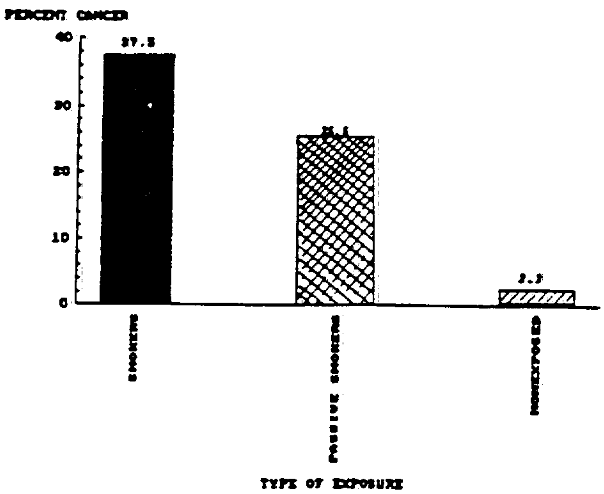

FIGURE 1. A comparison of mortality rates of smokers, passive smokers, and the nonexposed.

Table IV
Analysis Using Age-Adjusted Values for Cancer Sites (All Cancer, Digestive, and Passive Smoking-Associated Cancer) for the Three Major Nonsmoking Groups

Disease	Group	EXP	OBS	Probability
All cancer				
	Nonexposed	24.0	4	0.00002
	Exposed nonemployed	73.1	78	NS
	Exposed employed	70.6	108	0.001
Digestive Cancer				
	Nonexposed	9.3	1	0.002
	Exposed nonemployed	24.2	28	NS
	Exposed employed	20.4	38	0.01
Passive smoking-associated cancer				
	Nonexposed	9.2	0	0.0002
	Exposed nonemployed	35.7	34	NS
	Exposed employed	38.9	54	0.1

biased in the types of cancer deaths that would have occurred during these years. Analysis of the data of previous nonrespondents showed the same basic distribution of cancer deaths as the analysis of original respondents. Therefore, the data from this population study are likely to be representive of the actual population.

These data provide evidence that nonsmoking women exposed to cigarette smoke (generated by smoking husbands, other smokers in the household, or in outside activities) has a higher probability of dying of cancer of all kinds than women who have no known exposure, i.e., cancer mortality in nonsmoking Erie County wives with no known exposure to tobacco smoke is very low — only 2.2% vs. 25.5% for exposed women and 35.3% for smoking wives (Figure 1).

The data imply that the absence of passive smoking could lead to even lower rates of cancer mortality for the total population. Thus, these data indicate that passive smoking is very detrimental to the health of the nonsmoker.

The total proportion of deaths due to cancer for the 401 smoking and 906 nonsmoking wives in this study is 23.9%. This result is close to the proportion of deaths due to cancer for women in Erie County (21.8%) for the years considered in the study as reported in the Pennsylvania Department of Health — Division of Vital Statistics. This agreement suggests that the data are representative of the total population.

The observation that the nonsmoking employed wives had an odds ratio of 2.2 of dying of cancer when compared with exposed nonemployed wives suggests that workplace exposures may involve important hazards in addition to, or apart from, tobacco smoke. Over 80% of the employed wives in this study were either office workers, in sales occupations, teachers, or nurses, who (aside from the nurses) should have had little contact with carcinogenic agents other than tobacco smoke. The doubling of the rates of cancer for employed women compared with nonemployed women are in agreement with the data of Repace and Lowry[25] and the estimates made by Wells.[26] It may be that work place passive smoking exposure is higher than at home. Another possible explanation is that the employed wives may receive additional tobacco smoke exposure from smokers at home such as from their spouse, i.e., their husbands may be more likely to be smokers or heavy smokers.

Also of interest is the observation that only 8 deaths due to lung cancer were reported among the total of 727 passively exposed nonsmoking wives. Thus passive smoking does not result in large numbers of lung cancer cases when compared to active smoking. This difference is in agreement with the results of several studies by Hirayama,[10] Tricopoulos et al.,[11] and Correa et al.[12] showing two- to threefold increases in lung cancer for exposed vs. nonexposed wives and a much larger increase for smokers. In addition, a study by Miller[27] on the Amish — a nearly completely nonsmoking population — showed no lung cancer cases among either male and female nonsmokers for the Lancaster County, Pennsylvania, Amish for the 1970 to 1980 decade.

There were no reported deaths from lung cancer, breast cancer, genitourinary, or lymphatic cancer among wives with no known exposure to tobacco smoke among the total of 179 deaths in the nonexposed category. This contrasts with the distribution of cancer mortality for women in the general population of Erie County for the years under consideration: lung cancer — 12.7%; breast cancer — 20.7%, and lym-

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phatic cancer — 8.7%. These Erie County percentages of cancer causes by site are close to the national averages. Thus it appears that the types of cancer reported in the nonexposed group are very different from the types of cancer reported for both passive smoking and active smoking groups. While it has been shown that passive smoking causes some lung cancer cases, the amount is small compared with that of those who smoke.

Whether or not breast cancer is caused by active or passive smoking has become a controversial issue. Previously, it was thought that breast cancer was not active-smoking related. For example, no editions of the U.S. Surgeon General's Reports from 1964 to 1989 show any subsections devoted to active smoking and breast cancer. However, the Bibliography of Smoking and Health and Index Medicus provides reports of many studies on the topic of smoking and breast cancer. The most recent studies appear to be equally divided between those concluding that there is no overall positive association with active smoking and breast cancer[28-31] and those that conclude a positive and, in some cases, a significant association between active smoking and breast cancer.[32-35]

It has been only recently that studies have taken into account the potential effect of passive smoking and its possible association with breast cancer. Two of the most recent studies were completed by Sandler et al.[36] and Horton.[37] Two other major cancer categories have been reported as being associated with passive smoking exposure — lymphatic cancer, by Wells;[26] and cervical cancer, by Slattery et al.[38] The data from the present study agree with the studies noted above.

The possibility of passive smoking being associated with cancer sites was also verified by the highly significant values obtained after age adjusting for total cancer, digestive cancer, and the combined passive smoking-related cancer sites (refer to Table IV).

Since many studies during this decade have come to the conclusion that breast cancer is not smoking related, this new data might appear to be questionable. However, past studies failed to allow for such passive smoking categories as employed women and others smoking in the household. Therefore, the results of the NPSSH study should provide a more accurate estimate of passive smoking exposure.

A recent article by Bailar and Smith,[39] pointing to the continued increase in cancer mortality despite our apparent gains in early identification, as well as improvements in the treatment of cancer, shows that cancer is still increasing in the population. It may be that the cumulative long-term effects of both passive smoking and active smoking are continuing to have an impact on this increased cancer mortality. These issues have important implications for both the home and the workplace.

More research is needed to validate these observations. New studies require:

1. Better estimates of exposure to passive smoking. The nonsmoking category should exclude employed women, women exposed at home by individuals other than their spouse, and long-term exposure in outside nonemployed activities, as well as exposure at home by their spouse.
2. Long-term exposure information — preferably a minimum of 3 decades-to-lifetime exposure. Studies involving a few weeks or months or even a few years of exposure are inappropriate for an analysis of the true long-term impact of passive smoking.
3. Large enough samples to provide valid data.

For comparative purposes with the results of this study, the author would like to see more population studies instead of nonrandom or nonpopulation based samples in order to overcome the biases that are inherent in these types of sample designs.

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Lung Cancer in Women in the Niagara Region, Ontario: A Case-control Study

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A case-control study of the etiology of lung cancer in women was conducted in the Niagara Region of Ontario, because of local concerns about a high incidence of lung cancer. 51 female patients with lung cancer and 45 matched controls were interviewed. Information was collected about active and passive smoking, occupation and residential history.

There was a strong association between active cigarette smoking and lung cancer (ever/never odds ratio 10.0; p < .001) and 85% of the cases of lung cancer were attributed to active cigarette smoking. No other factors were significantly associated with lung cancer; there was weak evidence of an association between urban environment during childhood and lung cancer (p = 0.07). Associations between lung cancer and air pollution and residential history, were not demonstrated, contrary to public perception. Thus, a previously reported excess of lung cancer in Niagara females is most likely attributable to cigarette smoking.

Une étude de cas contrôlée sur l'étiologie du cancer du poumon chez la femme a été réalisée dans la région de Niagara (Ontario) en raison des préoccupations locales touchant l'incidence élevée de cette maladie dans la région. 51 patientes atteintes d'un cancer du poumon et 45 sujets témoins ont fait l'objet d'une entrevue. Des données ont été recueillies sur la consommation active et passive de tabac, l'occupation et le lieu de résidence des patientes et des sujets témoins.

La consommation active de cigarettes a été fortement associée au cancer du poumon (rapport consommation antérieure/aucune consommation de 10,0; p < 0,001) et 85% des cas de cancer du poumon ont été attribués à la consommation active de tabac. Aucun autre facteur n'a été associé de façon significative au cancer du poumon; un faible indice d'association entre la résidence en milieu urbain pendant l'enfance et le cancer du poumon a été constaté (p = 0,07). Contrairement à l'opinion générale répandue, aucune association n'a pu être établie entre le cancer du poumon et la pollution atmosphérique ou le milieu de résidence. La prévalence élevée du cancer du poumon chez les femmes de la région de Niagara signalée par le passé est donc vraisemblablement attribuable à la consommation de cigarettes.

In 1984, an exploratory study of cancer mortality in the Niagara Region of Ontario (Figure 1) reported a statistically significant excess of fatal lung cancer in Niagara women (but not men), compared with all Ontario women, over the interval 1976 to 1981.[5] Because of local concerns about this excess,[1] a case-control study of the etiology of lung cancer in Niagara females was initiated by the Niagara Health Services Department in 1984.

Tobacco smoking has been clearly established as the major cause of lung cancer in both sexes in North America. Over 40,000 reports and papers have been published about this association,[6-7] including over 40 case-control studies and at least 8 cohort studies. Most lung cancer in men and an appreciable proportion in women, is attributable to cigarette smoking (Table I).

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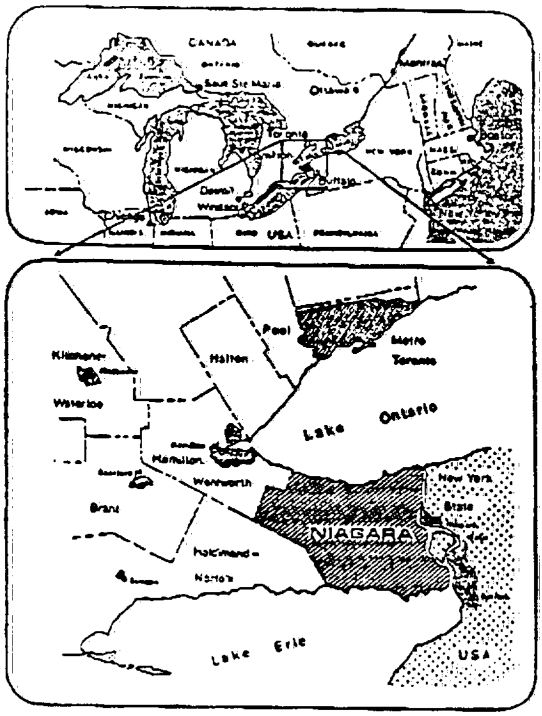

Figure 1. Niagara Region, Ontario. Total population (1981): 368,288.

Most of the analytic epidemiologic studies of the association between smoking and lung cancer have been conducted in densely populated urban areas; few have been conducted in less densely populated areas such as the Niagara Region.

Evidence supporting a causal association between lung cancer and occupation is fairly strong for certain occupations and substances, including underground hematite mining, nickel refining, uranium mining, soots and tars, asbestos, arsenic and chromium. Evidence is suggestive for several other substances and occupational groups. There is also suggestive evidence of an association between lung cancer and passive smoking.

Evidence concerning a causal association between air pollution and lung cancer is weak and conflicting, but air pollution remains plausible as a cause of lung cancer because: (a) there is an urban factor for lung cancer that may not be completely explained by smoking habits and occupational exposures; (b) there is strong evidence from occupational studies that prolonged and heavy exposure to certain airborne substances (e.g. soot, tar, benzo(a)pyrene, asbestos, vinyl chloride) may cause lung cancer; and (c) there is weak evidence from ecologic and other observational studies suggesting a quantitative relationship between ambient air pollution levels and lung cancer.

TABLE I
Population Attributable Risk Percent for Cigarette Smoking and Lung Cancer for Women and Men from Case-control and Cohort Studies

Study population (years of enrolment ± follow-up)	PAR% Women	Men
U.S.A. – 1958/9 case-control	25%	64%
U.S.A. – 1959/72 cohort	36%	83%
U.K. physicians – 1951/73 cohort	67%	92%
Japan – 1965/74 cohort	24%	72%
Western Europe – 1976/80 case-control	48%	85%
England – 1977/82 case-control	73%	89%
Los Angeles – 1981/82 case-control	75%	–
Western N.Y. State – 1980/84 case-control	71%	58%

We report the findings of a case-control study about the possible etiologic association between the above factors (i.e. tobacco smoking, ambient air pollution, passive smoking and occupational exposures) and lung cancer among female residents of Niagara Region.

METHODS

Female residents of Niagara who were newly diagnosed with primary lung cancer between January 1, 1983 and March 31, 1985, and who were under 75 years of age at diagnosis, were eligible. Cases were identified through chart reviews at 7 of 9 public hospitals in Niagara (two hospitals refused to participate), and at the major referral hospitals in Toronto. 72 eligible cases were identified. Of these, attending physicians refused permission to contact 3, 6 could not be located or had moved out of the region, and 12 refused to be interviewed. Thus, 51 cases, representing 71% of eligible cases identified for this study, were interviewed. Of those cases participating in the study, histologic confirmation was available for 88% (45/51).

At the time of interview, 53% (27/51) of cases were alive. In the event of death, next-of-kin were interviewed.

Female controls were randomly selected from the municipal assessment lists for 1983 and 1984. They were individually matched to cases on the basis of age (within 4 years), and municipality of residence at one year prior to the date of diagnosis of the corresponding case. Matching on municipality (i.e. city, town, township) was necessary because 2 of 9 public hospitals in Niagara refused to participate, leading to substantial under-enumeration of cases from certain municipalities. In the event that an eligible control could not be located or refused to participate, a second eligible control was selected in the same manner as the first.

Of 97 potentially eligible controls selected, 20 (21%) could not be located or had moved out of Niagara Region. Of the 77 eligible controls contacted, 45 (58%) agreed to participate in the study. All controls were alive at the time of interview, but one was too ill to be interviewed, and a proxy was interviewed instead.

TABLE II
Age-adjusted Odds Ratios for Lung Cancer in Niagara Women in relation to Cigarette Smoking Status

Cigarette Smoking Status*	Odds Ratio (95% CI)	Number of Cases/Controls
Never smoker	1.0	5/27
Ever smoker	10.0 (3.5-42.)	46/18
Ex-smoker	1.6 (0.28-9.0)	6/10
Current smoker	35.0 (7.5-340.)	40/8

* Status at one year prior to date of diagnosis of case.

Cases and controls were interviewed in their own homes by an experienced interviewer, using a standardized questionnaire. Information was collected on lifetime residential and occupational history, lifetime tobacco smoking history, exposure to passive tobacco smoke, personal and spousal exposure to occupational substances and suspect industries, and various socio-demographic variables.

Statistical analysis was conducted mainly by multivariate logistic regression modelling. Subject matching used in the design was preserved in the analysis. Because 6 of the cases could not be individually matched to controls, they were matched to controls within existing matched pairs to create 6 matched triplets. The PECAN computer program,[7] which permits analysis where there is a variable number of subjects within each matched set, was used to derive conditional maximum likelihood estimates of the parameters. Because of the relatively small number of subjects in some of the exposure categories, confidence intervals were calculated using the log likelihood-based procedure.[8]

RESULTS

Socio-demographic Variables

As expected, there was no significant difference in age, comparing cases with controls. The mean age (at diagnosis) of cases was 60.8 years and the mean age of controls was 60.4 years. Current annual family income, marital status and religion were found to be comparable between cases and controls.

TABLE III
Trends in Age-adjusted Odds Ratios for Lung Cancer, in relation to Smoking Exposures considered as Continuous Variables

Continuous Smoking Variables*	Odds Ratio† (95% CI)
Duration smoked (per 10 years)	1.97 (1.48-3.1)
Average frequency (per 20 cigarettes/day)	23.0 (5.6-190.)
Current frequency (per 20 cigarettes/day)	8.1 (3.2-27.)
Lifetime consumption (per 20 pack-years)	6.7 (2.6-32.0)
Age started smoking‡ (per 10 years)	0.54 (0.25-1.10)
Years since quitting (per 10 years)	0.16 (0.028-0.48)

*status at one year prior to date of diagnosis of case.
†corresponding to the unit of change specified for each variable.
‡as adjusted for average frequency (cig./day)

Active Cigarette Smoking

Cigarette smoking was strongly associated with risk of lung cancer in Niagara women (Table II). Strong risk gradients were seen when tobacco smoking was represented by continuous variables (Table III).

Ex-smokers (defined as smokers who quit smoking at least one year prior to the date of diagnosis of the case) had a risk of lung cancer significantly less than current smokers (OR = 0.05; 95% CI = 0.002-0.30). In comparison to non-smokers, their risk was elevated, but this finding was not statistically significant (OR = 1.6; 95% CI = 0.28-9.0). For ex-smokers, their risk decreased with increasing time since quitting (Table III).

Population attributable risk (PAR) was estimated for cigarette smoking, using lifetime consumption (pack-years) and assuming a monotonic multiplicative model.[9] The estimate of PAR was 85%, mostly due to current smoking (80%), rather than ex-smoking (5%).

Passive Smoking (Environmental Tobacco Exposure)

Overall, 90% (46/51) of cases and 78% (35/45) of controls reported some past exposure to passive tobacco smoke in their homes. After adjustment for personal lifetime cigarette con-

TABLE IV
Adjusted Odds Ratios for Lung Cancer, in relation to Passive Smoking

Exposure*	Odds Ratio† (95% CI)	Number of Cases/Controls
Anyone in same household ever smoked	3.6 (0.39-38.)	46/35
Mother ever smoked	0.76 (0.06-8.3)	7/5
Father ever smoked	0.67 (0.15-2.7)	19/23
Husband ever smoked‡	1.04 (0.27-4.1)	36/25
Ever exposed in workplace§	0.57 (0.11-2.7)	14/12

*status at date of diagnosis of case.
†with adjustment for lifetime consumption of cigarettes (pack-years), and using "never" category as baseline.
‡never-married subjects were excluded.
§subjects who had never worked outside of the house were excluded.

TABLE V
Adjusted Odds Ratios for Lung Cancer in relation to Residential History

Residential History*	Odds Ratio† (95% CI)	Number of Cases/Controls
Duration lived in Niagara Region		
<40 years	1.0	22/28
>40 years	6.1 (0.96-102.)	29/17
cont.‡ (per 10 years)	1.22 (0.82-2.4)	
Childhood residence		
country/small town	1.0	20/29
large town/city	7.8 (0.62-98.)	31/16
Adult Residence		
country/small town	1.0	14/16
large town/city	2.3 (0.49-13.7)	37/29

*status as of one year prior to date of diagnosis.
†including adjustment for lifetime cigarette consumption (pack-years)
‡continuous variable, with OR corresponding to the unit of change specified

TABLE VI
Exposure to A Priori Suspect Occupations

Suspect Industries	Study Subjects Cases/Controls	Spouses of Study Subjects Cases/Controls
1. Asbestos mining, Mfg., or Use	0/1	
2. Asphalt Paving		3/0
3. Beautician/Hairdresser	1/1	
4. Beryllium Mining		
5. Bricklayer		2/1
6. Ceramic/Enamel Products		
7. Chemical Industry		2/3
8. Chromium Mining or Mfg.	1/0	
9. Cobalt Mining/Refining		
10. Coke Oven Worker		0/1
11. Construction		6/6
12. Copper Mining/Smelter		1/0
13. Dental Technician		
14. Fire Brick Plant Worker		1/0
15. Furnace Boiler Work		
16. Garage/Filling Station		4/4
17. Iron Mining		
18. Laundry/Dry Cleaning	0/1	
19. Maintenance Work/Sup't	1/1	4/1
20. Newsprinter		1/0
21. Nickel Refinery		4/6
22. Painter/Paint Factory	0/1	2/1
23. Plastics Factory		1/1
24. Rubber Mfg., or Use		
25. Sheet Metal Work	1/0	5/2
26. Ship Yard		5/0
27. Soap Factory	1/0	0/1
28. Steel Industry	0/1	4/5
29. Talc Manufacture		
30. Textile Products	4/1	
31. Transport Industry		8/2
32. Uranium Mining		0/1
33. Wearing Heat Protective Clothing	1/0	2/0
34. Woodworking		
35. Zinc Mining		

sumption, there was insufficient statistical evidence supporting an association between tobacco smoke in the household and lung cancer (OR = 3.6; p = 0.24). Further, there was no association between lung cancer and having a mother, father or husband who smoked in the same household (Table IV). Passive smoking in the household was also examined in terms of duration (years) that each subject reported exposure as a child, and as an adult. Neither exposure was significantly associated with risk after adjusting for active smoking. There was no evidence that passive smoking exposure in the workplace was associated with lung cancer.

Environmental Exposure and Residential History

Because of the absence of a more direct measure of exposure, residential history was used as a measure of exposure to ambient air pollution, and to the more important industrial point sources of air pollution in Niagara Region.

There was some evidence of an association between long duration of residence in Niagara (40 years or more) and risk of lung cancer (OR = 6.1; p = 0.06), but there was insufficient evidence of a risk gradient (p = 0.32) (Table V). There was evidence of a statistically significant interaction between smoking (pack-years) and duration lived in Niagara (p = 0.03). When this interaction term (pack-years X years lived in Niagara) was included in the model, there was no change in the estimated effect of the primary variable pack-years, but the estimated effect of the primary variable "duration lived in Niagara" reversed (OR = 0.88 per 10 years lived in Niagara; p = 0.68).

There was weak evidence of an association between urban living in childhood (prior to age 21) and lung cancer, after adjusting for lifetime cigarette consumption (Table V). This association did not change appreciably when the model was adjusted for adult residence or duration lived in Niagara.

A significant association was not found between adult urban living and risk of lung cancer (Table V). The effect was further weakened when the model was also adjusted for childhood residence (OR = 1.4; p = 0.74).

Twelve major point sources of air pollution were identified in or around Niagara, including sources in Hamilton, Buffalo and Niagara Falls, New York.[44] No significant association was found (p = 0.65) between lung cancer and distance of residence (one year prior to diagnosis) to the nearest point source (3 levels: < 2 km; 2-4 km; > 4 km). When distance was examined as a continuous variable, there was also no statistically significant association (OR = 1.04 per kilometer; p = 0.74). Residential distance 10 years prior to diagnosis also showed no evidence of an association with lung cancer.

Occupational Factors

No risk was associated with employment outside the home (OR = 0.57; 95% CI = 0.06-4.05), or with exposure to dust or fumes, in the workplace (OR = 0.92; 95% CI = 0.24-3.4). Concerning employment in 35 a priori suspect occupations (Table VI), there was no association between any of these and lung cancer. Concerning exposure to any of 11 a priori suspect substances (Table VII), no statistically significant associations were found. The occupational history of spouses was also examined, but there were no statistically significant associations with lung cancer.

DISCUSSION

A number of caveats should be considered before conclusions are drawn from this study. First, because of the small study size, power considerations set some limitations on the identification of important differences between cases and controls. For example, in a study of this size, the power in detecting a statistically significant (i.e. $\alpha = .05$ two-tailed) two-fold difference in risk is 38%; the power in detecting a three-fold difference in risk is 73%. For this reason, the confidence limits of the estimates of effect are wide. This limitation is likely

TABLE VII
Exposure to A Priori Suspect Substances

Suspect Substances	Study Subjects Cases/Controls	Spouses of Study Subjects Cases/Controls		Study Subjects Cases/Controls	Spouses of Study Subjects Cases/Controls
1. Arsenic	0/0	0/0	7. Methanol	0/0	0/0
2. Asbestos	0/1	2/2	8. Polycyclic Aromatic Hydrocarbons	0/0	0/0
3. BCME/CMME	0/0	0/0	9. Radioactive Material	0/0	0/2
4. Coal/Charcoal	0/1	2/5	10. Silica	0/1	2/1
5. Coal Tar	0/0	2/2	11. Talc	1/1	2/1
6. D.D.T.	0/1	1/2			

to be a problem in most studies evaluating rather localized concerns, and does not necessarily prohibit such studies.

Second, because only 71% of eligible cases and 58% of located controls participated in this study, the results cannot easily be generalized to the total female population of Niagara. However, there were no significant differences in age or histologic type of lung cancer, comparing participating cases with all eligible cases.[1] Unfortunately, there was no information about smoking habits (or other possible risk factors) for non-participating cases.

Comparison of study controls with women 45 to 74 years of age who were interviewed in Niagara's Community Health Survey in 1985,[1] demonstrated that the study controls had less formal education, and a higher proportion were married, had U.K. ancestors and were currently working. Also the proportion of ever smokers was somewhat lower in study controls than in survey females (40% vs. 49%).[1] This difference could have inflated the estimate of the smoking effect somewhat, but it is unlikely to have altered the main conclusions of the study.

And third, because of the retrospective recruitment of most cases, approximately half of eligible cases were dead by the time of the interview. These subjects were retained in the study, and proxies were interviewed instead. Recent work on the reliability and validity of respondent information in a case-control study of lung cancer suggests that good agreement can be expected between proxies and cases in terms of basic smoking status (i.e., never, ex-, current), and daily frequency of smoking.

In spite of the foregoing considerations, there is good evidence of a strong association between cigarette smoking and lung cancer in Niagara women. The point estimate of the effect of ever smoking (OR = 10.0) is among the highest reported values associated with ever smoking, in women. Similar risks have been found in the much larger companion study of the NCIC Epidemiology Unit, conducted over a similar period, and in a recently published cohort study. There is evidence that women are now smoking more intensely, and for a longer duration, than in years past; thus, it is not surprising that the risk in smoking women is now similar in magnitude to the risk reported in smoking men from earlier studies. It is likely that these higher risks now being reported for women will continue to be found in the future.

The PAR estimate for lung cancer associated with cigarette smoking in Niagara women was 85%. This estimate was higher than that derived from previously published studies (see Table 1). Most of this PAR was associated with current smoking (80%), rather than ex-smoking (5%). There can be little doubt that most lung cancer in Niagara women is now attributable to active cigarette smoking.

There was insufficient statistical evidence from this study to support a strong association between lung cancer and other study variables, including passive smoking, environmental exposure, residential history and occupational factors. The presence of an "urban factor", at least for the childhood years, was suggested in this study. However, it is known that urban living is associated with an earlier age of onset of smoking. It is possible that we were unable to control completely for the smoking effect when studying this "urban factor".

Contrary to popular perception,[1] there is little evidence that general ambient air quality is poor in Niagara Region, compared with other urban and semi-urban areas in Ontario. In terms of the Air Pollution Index calculated for nine cities in Ontario, St. Catharines and Niagara Falls report the lowest average levels. Both St. Catharines and Niagara Falls are considered by the Ontario Ministry of the Environment to have good ambient air quality, although local problems have been identified over the years.

In terms of local sources of pollution, distance of residence to the nearest industrial point source of air pollution did not appear to be related to risk. Small study size precluded analysis of individual point sources. Distance to the nearest point source may not be the best indicator of environmental exposure, either, as it fails to take into account wind direction and other climatic variables.

Matching cases and controls on municipality of residence may have resulted in over-matching on distance to the nearest point source of pollution. Atmospheric concentration of particulates emitted from industrial point sources decreases logarithmically with distance from the source, with highest concentration within 2 km. of the source, and with levels reaching background values at 4-5 km. from the source. In this study, 38% (37/96) of subjects lived within 2 km. of the nearest industrial point source, 36% (35/96) lived within 2-4 km., and 25% (24/96) lived more than 4 km. from the nearest point source. Thus, there was good variation in the distance of Niagara subjects to point sources and no real evidence of over-matching on this variable.

The previously reported excess of fatal lung cancer in Niagara females[5] is most likely attributable to active cigarette smoking. This study failed to demonstrate a strong association between air pollution or residential history and risk of lung cancer.

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Indoor Air Pollution and Lung Cancer in Guangzhou, People's Republic of China

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A case-control study comprising 224 male and 92 female incident lung cancer cases and the same number of individually matched hospital controls was conducted from June 1983 to June 1984 in Guangzhou, People's Republic of China, to evaluate the association between indoor air pollution and lung cancer risk. Guangzhou residents were exposed to several sources of pollution in their homes, most importantly to cooking fumes. Increased risks were found among subjects living in a house without a separate kitchen (the exposure odds ratio was 2.4 (95% confidence interval (CI) 1.4–4.2) for men and 5.9 (95% CI 2.1–16.0) for women). Similarly, living in a house with poor air circulation was associated with an exposure odds ratio of 2.1 (95% CI 1.2–3.8) for men and 3.6 (95% CI 1.4–9.3) for women. A trend in the association between lung cancer risk and factors pertaining to house and kitchen ventilation was observed, and a decreasing risk of lung cancer was observed for several variables indicating better ventilation, even after adjustment for potential confounders such as education, occupation, living area, smoking, and history of chronic respiratory diseases. No statistically significant differences were found between cases and controls for frequency of cooking at home, presence of a chimney in the kitchen, or type of cooking fuel. Smoking was clearly related to risk of lung cancer in both men and women, and among nonsmoking women, exposure to tobacco smoke from their spouses was also associated with an increased risk. These results suggest that, in addition to smoking, indoor air pollution may be a risk factor for lung cancer. *Am J Epidemiol* 1993;137:145–54.

air pollutants, environmental; lung neoplasms; smoking; tobacco smoke pollution; ventilation

Lung cancer is the major cause of cancer death for both men and women in Guangzhou, the main city in the Guangdong province of the People's Republic of China, representing about one fourth of all cancer deaths in that city. During the period 1981–1984, the crude mortality rates for lung cancer in the Guangzhou metropolitan area were, respectively, 45 male deaths and 24 female deaths per 100,000 person-years (1). Although smoking is the most important cause of lung cancer (2–4), smoking behavior cannot fully explain the epidemiology of lung cancer in Chinese women, in whom there is a rather high incidence of lung cancer, predominantly adenocarcinoma, de-

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Abbreviation: CI, confidence interval.

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spite relatively low smoking rates (5–12). The male:female ratio of lung cancer incidence is about 2 in China (1, 13), even though there is a much bigger difference than that in smoking rates between men and women. In contrast, this ratio varies from 4 to 10 in Western Europe and is about 2 in the United States (13), but with a much higher prevalence of current and former smokers among American women.

During the last decade, increasing attention has been paid to the health effects of the indoor microenvironment. Some studies have shown a positive relation of passive smoking to lung cancer risk (14–18), as well as an association with exposure to radon and its decay products (19–25). However, research results for other sources of indoor air pollution, such as cooking and heating, have been rather elusive and inconclusive (26–29). The goal of this study was to evaluate whether there is any relation between indoor air pollution resulting from domestic cooking practices and lung cancer occurrence.

MATERIALS AND METHODS

Newly diagnosed cases of primary lung cancer (*International Classification of Diseases*, Ninth Revision, code 162) were selected from eight major hospitals covering most of Guangzhou from June 1983 to June 1984. All cases occurred in permanent residents of the city of Guangzhou. A total of 327 lung cancer cases were identified from the medical records of these eight hospitals during that year. It was possible to complete an interview for 316 cases (224 men and 92 women; 96.6 percent). Eleven cases were excluded because either they were too ill to answer the interview, they could not be traced, or they had already died. Fifty-five percent of cases were diagnosed by means of repeated chest radiographic examinations and clinical examination; 13 percent were diagnosed by bronchoscopy alone; and 32 percent of the cases had cytologic or histologic confirmation.

Controls who were also permanent residents of the city of Guangzhou were individually matched to cases on age (to within 2 years), sex, residential district (Liwan, Yuexiu, Haizhu, or Dongshan), and date of diagnosis or hospital admission. Controls were selected according to the matching criteria among inpatients of the surgery departments at six of the same eight major hospitals. No controls were chosen from either the Tumor Hospital or the Chest Hospital. Patients who had been admitted for chronic obstructive diseases of the lung, pulmonary tuberculosis, malignant tumors, and coronary heart disease were excluded. Each control was to be interviewed during the 2 months following the interview of his/her matched case. In most instances, the first selected patient control was interviewed; only for 26 subjects were second-choice controls chosen because of an inability to trace the subject or because an individual was found to be inadequate regarding one or several of the matching variables. No subject refused the interview.

The interview was carried out at the subject's home by trained epidemiologic workers using a structured questionnaire. All cases and controls were interviewed in person. The interviewers obtained extensive information about the subject's general demographic characteristics, occupational history, history of respiratory diseases, family cancer history, smoking habits, spouse's smoking habits, cooking practices (including domestic fuel use), and residence history. After completing the questionnaire, the interviewer measured the size of the windows and doors that opened onto the outside of the building, thereby providing an estimation of ventilation capacity. The ventilation capacity of the kitchen was analyzed separately from that of the rest of the dwelling, hereafter designated the living area. If the subject had lived in his or her present home for less than 20 years, the interviewer asked similar questions regarding the preceding residences and their ventilation conditions. In the latter case, given that no measurements were available, the ventilation conditions of previous residences were simply ranked as poor, average, or good based on the questionnaire data. Data on up to three residences were collected; however, since the

population of the People's Republic of China is relatively stable, very few subjects had moved more than twice.

Exposure odds ratios, their 95 percent confidence intervals, and significance levels were computed using a matched-pair analysis method (30). A conditional logistic regression model was used to estimate exposure odds ratios for multiple class variables and to adjust for confounding factors. The SAS (31) and EGRET (32) software packages were used for the analysis.

RESULTS

Table 1 presents the demographic characteristics of lung cancer cases and controls. The ages of cases ranged from 28 years to 83 years, but the majority of cases were in their fifties or sixties. The median ages of male and female cases were 62 years and 60.5 years, respectively. The median ages of male and female controls were 62 and 61.5. Almost all subjects were of Han nationality, and most subjects had been born in the province of Guangdong. Marital status, educational level, dialect, occupation, and living area did not differ significantly between cases and controls, although cases had a lower educational level and a smaller average living area than controls. Thus, we controlled for education, occupation, and living area when we analyzed other variables.

TABLE 1. Demographic characteristics of lung cancer cases and controls, Guangzhou, People's Republic of China, 1983–1984

Characteristic	Men				Women			
	No. of cases	%	No. of controls	%	No. of cases	%	No. of controls	%
Age (years)								
<40	2	0.9	3	1.3	1	1.1	1	1.1
40–49	13	5.8	12	5.4	9	9.8	10	10.9
50–59	76	33.9	80	35.7	33	35.9	33	35.9
60–69	90	40.2	84	37.5	24	26.1	23	25.0
≥70	43	19.2	45	20.1	25	27.2	25	27.2
Marital status								
Married	193	86.2	194	86.6	56	60.9	53	57.6
Widowed	27	12.1	24	10.7	36	39.1	33	35.9
Divorced	3	1.3	4	1.8	0	0.0	0	0.0
Single	1	0.4	2	0.9	0	0.0	6	6.5
Years of education								
<1	22	9.8	10	4.5	40	43.5	41	44.6
1–6	139	62.1	134	59.8	35	38.0	35	38.0
7–12	50	22.3	60	26.8	17	18.5	16	17.4
≥13	13	5.8	20	8.9	0	0.0	0	0.0
Province of birth								
Guangdong	207	92.4	206	92.0	80	87.0	83	90.2
Other	17	7.6	18	8.0	12	13.0	9	9.8
Occupation								
Worker	152	67.8	153	68.3	59	64.1	55	59.8
Other	70	31.3	67	29.9	11	12.0	13	14.1
None	2	0.9	4	1.8	22	23.9	24	26.1
Living area (m^2 per person)								
<2.00	11	4.9	6	2.7	2	2.2	2	2.2
2.00–3.99	56	25.0	42	18.7	27	29.3	15	16.3
4.00–7.99	100	44.6	109	48.7	38	41.3	42	45.6
≥8.00	57	25.5	67	29.9	25	27.2	33	35.9

TABLE 2. History of occupational exposure and personal and familial history of selected diseases among lung cancer cases and controls, Guangzhou, People's Republic of China, 1983–1984

Exposure	Men					Women				
	No. of cases	No. of controls	EOR_1*	EOR_2*	95% CI*	No. of cases	No. of controls	EOR_1	EOR_2	95% CI
History of occupational exposure										
None†	151	184	1.0	1.0		69	78	1.0	1.0	
Dust	20	8	2.6	2.2	0.78–6.2	13	4	4.3	8.8	1.6–46.6
Smoke	23	12	2.1	2.1	0.89–5.1	1	2	0.74	0.57	0.00–73.4
Other	30	20	1.7	1.6	0.72–3.5	9	8	1.5	1.0	0.26–4.2
History of pulmonary tuberculosis										
No†	137	176	1.0	1.0		78	85	1.0	1.0	
Yes	87	48	2.8	2.4	1.3–4.6	14	7	2.2	1.3	0.39–4.3
History of chronic bronchitis										
No†	125	185	1.0	1.0		63	79	1.0	1.0	
Yes	99	39	3.9	3.0	1.6–5.5	29	13	2.6	0.90	0.36–2.4
Family history of cancer										
No†	203	216	1.0	1.0		83	86	1.0	1.0	
Yes	21	8	2.9	0.90	0.62–1.3	9	6	1.5	0.94	0.54–1.6

* EOR_1, matched exposure odds ratio; EOR_2, matched logistic exposure odds ratio, adjusted for education, occupation, living area, and smoking; CI, confidence interval.

† Referent.

As expected, the subjects with lung cancer showed increased frequencies of occupational exposure to hazardous working environments, a history of pulmonary tuberculosis, and a history of chronic bronchitis in both sex groups (table 2). When education, occupation, living area, and smoking were controlled for, the associations of lung cancer with the above risk factors were not substantially modified among men, but they were attenuated or even disappeared among women, except for exposure to dust. In contrast, the increased risk of lung cancer associated with a family history of cancer, found in univariate analysis, disappeared for both men and women when we controlled for the same variables. Smoking was strongly related in a dose-response manner to the risk of lung cancer in both men and women (table 3). Ninety-five percent of male cases and 59 percent of female cases had ever smoked, compared with 80 percent and 25 percent of male and female controls, respectively. The exposure odds ratios for lung cancer were 6.3 (95 percent confidence interval (CI) 2.7–15.0) and 4.9 (95 percent CI 2.3–10.4) among male and female smokers, respectively. An increased risk of lung cancer was also observed among nonsmoking women who lived with a husband who smoked the equivalent of 20 or more cigarettes per day (table 3).

Table 4 presents information on the cooking practices of lung cancer cases and controls. Results showed that women bore the primary burden of cooking in the family. The majority of families cooked three times per day at home, and coal was the basic cooking fuel used. Questions were asked on the type of fuel used during three historical periods (1949–1957, 1958–1976, and 1977 to the present). Since cooking fuel is rationed by the government, there was little variation in fuel usage among families in Guangzhou. Before 1958, most families used wood and charcoal. From 1958 to 1976, they gradually turned to coal, and gas was used only after 1976. Results are presented for the most recent period, which is the only one in which differences between cases and controls could be distinguished. The history of coal use in Guangzhou was usually longer than 20 years, and only in the past 3–5 years had a small proportion of families changed to petroleum gas as a domestic fuel. Very few families used mainly electricity or kerosene

TABLE 3. Exposure to smoking among lung cancer cases and controls, Guangzhou, People's Republic of China, 1983–1984

Exposure	No. of cases	No. of controls	EOR*	95% CI*
Active smoking (cigarette equivalents smoked per day) among men				
Never smoker†	12	44	1.0	
1–19	21	93	1.2	0.43–3.5
20–29	97	66	7.1	2.6–19.5
≥30	94	21	21.4	7.1–64.0
χ^2 for trend = 99.6 $p < 0.001$				
Active smoking (cigarette equivalents smoked per day) among women				
Never smoker†	38	69	1.0	
1–9	8	10	1.8	0.57–5.9
10–19	16	9	3.5	1.2–9.8
≥20	30	4	17.9	4.0–80.6
χ^2 for trend = 28.0 $p < 0.001$				
Passive smoking among nonsmoking women (cigarette equivalents smoked per day by husband)‡				
Not exposed†	13	32	1.0	
1–19	6	21	0.7	0.23–2.2
≥20	19	16	2.9	1.2–7.3
χ^2 for trend = 4.5 $p = 0.034$				

* EOR, matched logistic exposure odds ratio, adjusted for education, occupation, and living area, comparing never smokers to present and former smokers combined; CI, confidence interval.
† Referent.
‡ Unmatched method was used.

for cooking. In the kitchens of more than 60 percent of families, there was no chimney or other apparatus for extracting fumes. No significant case-control differences were associated with the above variables.

Information on the use of cooking oil was not formally included in our study. In the People's Republic of China, cooking oil is rationed by the government-controlled food and oil company, and in Guangzhou, the main cooking oil used is peanut oil (for a short time it was bean oil). Rapeseed oil was not widely available, and we did not expect to find any differences in the types of oil being used, because all Guangzhou residents are dependent on the same government supply.

Analysis of the effect of ventilation conditions on lung cancer risk was conducted for housing at the time of diagnosis and interview, as well as housing where subjects had lived the longest; finally, data were summarized over all residences. The results of these analyses were similar (data not shown); therefore, this paper presents only the results of the analysis for current ventilation conditions. In addition, the proportions of cases and controls who had moved during the past 10 or 20 years did not differ significantly, and duration of residence in the current housing was similar for cases and controls. For most subjects, the current residence was also the longest residence.

Table 5 shows that after adjustment for education, occupation, occupational exposure, pulmonary tuberculosis history, chronic bronchitis history, family cancer history, amount of smoking per day, and living area, as well as passive smoking (for women only), several variables pertaining to ventilation conditions were strongly associated with lung cancer risk. There was increased risk associated with having a window or door opening from the kitchen directly into the living area or bedroom, and for cooking in the living area or bedroom. For cooking in the living area or bedroom, the exposure odds ratio was 2.4 (95 percent CI 1.4–4.2) for men and 5.9 (95 percent CI 2.1–16.0) for women. Having windows or doors that opened in different directions so that indoor air could circulate also significantly influenced the risk of lung cancer. The relative risk for lung cancer tended to decrease with increasing size of ventilation openings in living areas and kitchens. For the best ventilated living area as compared with the least ventilated, the exposure odds ratio for lung cancer was reduced to only 0.14 (95 percent CI 0.04–0.51) for men and 0.02 (95 percent CI 0.00–0.21) for women. The exposure odds ratios for kitchen ventilation were 0.15 (95 percent CI 0.05–0.44) for men and 0.06 (95 percent CI 0.01–0.32) for women, respectively. The differences were statistically significant. A similar trend was found for the ceiling height throughout the apartment, but no clear trend was seen for the floor on

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TABLE 4. Cooking practices of lung cancer cases and controls, Guangzhou, People's Republic of China, 1983–1984

Cooking practice	Men					Women				
	No. of cases	No. of controls	EOR_1*	EOR_2*	95% CI*	No. of cases	No. of controls	EOR_1	EOR_3*	95% CI
Frequency of cooking at home										
Rarely†	107	100	1.0	1.0		4	5	1.0		
Occasionally	45	63	0.65	0.52	0.25–1.1	8	8	1.2	1.2	0.17–9.2
Frequently	72	61	1.1	1.1	0.69–1.9	80	79	1.3	1.1	0.19–6.1
Having a chimney in kitchen (years)										
No chimney†	160	147	1.0	1.0		56	54	1.0	1.0	
1–9	33	37	0.80	0.55	0.22–1.6	16	10	1.7	3.6	0.72–17.5
≥10	31	40	0.70	0.80	0.34–1.9	20	28	0.77	1.1	0.40–3.0
Cooking fuel										
Coal†	200	193	1.0	1.0		81	79	1.0	1.0	
Gas	14	22	0.59	0.48	0.15–1.6	8	9	0.90	0.90	0.24–3.3
Wood	8	9	0.79	0.57	0.11–3.0	3	4	0.67	0.67	0.04–11.7
Other	2	0				0	0			
No. of meals prepared at home per day										
0–1†	18	26	1.0	1.0		2	3	1.0	1.0	
2	26	33	1.2	0.83	0.27–2.6	7	12	0.67	0.48	0.03–8.8
3	180	165	1.7	1.3	0.50–3.3	83	77	1.5	1.5	0.12–17.7

* EOR_1, matched exposure odds ratio; EOR_2, matched logistic exposure odds ratio, adjusted for education, occupation, occupational exposure, history of tuberculosis, chronic bronchitis, family history of cancer, smoking, and living area; CI, confidence interval; EOR_3, matched logistic exposure odds ratio, adjusted for passive smoking in addition to all of the variables listed above.

† Referent.

which the subject lived, with the exception of a higher risk for people living on the ground floor as opposed to a higher floor. When we analyzed the effect of floor by district of residence and by sex, we found the higher risk for persons living on the ground floor in three out of four districts for women and in two out four districts for men (data not shown).

DISCUSSION

Usually, hospital controls are selected from the same hospitals as the cases, but in this study some of the controls were not chosen from the same hospital as their matched cases because two of the hospitals that were sources of cases were deliberately excluded as sources of controls. We did this to avoid selection of subjects with diseases that could potentially be linked to smoking and/or air pollution. To reduce potential bias in the control selection procedure, we matched cases and controls on district of residence, thereby controlling for the referral pattern of patients. Most importantly, this matching also controlled for atmospheric air pollution. Results of environmental surveillance were only available at the district level, as were lung cancer mortality rates. One district, Liwan, has the highest levels for all indexes of air pollution (falling dust, benzo(*a*)pyrene, total suspended particulate matter, sulfur dioxide, nitrogen oxide, and carbon monoxide), whereas the other three districts do not differ from one another appreciably (33). The highest age-standardized (world standard population) lung cancer mortality rates for women are recorded in Liwan at 22.2 deaths per 100,000 woman-years, compared with the lowest rate for the district of Dongshan at 18.3. For men, the highest mortality rate is in Yuexiu at 51.8, versus the lowest rate in Dongshan at 40.9. All of the pairs of cases and controls lived in the same residential district, in an area of about 10 km^2. They were exposed to approximately similar levels of outdoor air pollution, although variations may have occurred within districts. No data were avail-

TABLE 5. Ventilation conditions in the homes of lung cancer cases and controls, Guangzhou, People's Republic of China, 1983–1984

Ventilation factor	Men					Women				
	No. of cases	No. of controls	EOR_1*	EOR_2*	95% CI*	No. of cases	No. of controls	EOR_1	EOR_3*	95% CI
Separate kitchen										
Yes†	72	113	1.0	1.0		29	52	1.0	1.0	
No	152	111	2.0	2.4	1.4–4.2	63	40	3.1	5.9	2.1–16.0
Good air circulation										
Yes†	90	120	1.0	1.0		38	60	1.0	1.0	
No	134	104	1.7	2.1	1.2–3.8	54	32	3.0	3.6	1.4–9.3
Size of ventilation openings in living area (m^2 per person)										
0.0–0.4†	47	48	1.0	1.0		16	6	1.0	1.0	
0.5–0.9	86	69	0.53	0.39	0.14–1.1	36	23	0.69	0.36	0.09–1.5
1.0–1.9	38	53	0.33	0.30	0.10–0.91	22	24	0.40	0.25	0.05–1.1
2.0–3.9	22	30	0.33	0.24	0.06–0.90	9	13	0.24	0.14	0.02–0.89
≥4.0	31	24	0.28	0.14	0.04–0.51	9	26	0.11	0.02	0.00–0.21
χ^2 for trend			14.5 ($p < 0.001$)					18.0 ($p < 0.001$)		
Size of ventilation openings in kitchen (m^2 per family)										
0.0–0.4†	79	41	1.0	1.0		22	8	1.0	1.0	
0.5–0.9	58	52	0.55	0.77	0.36–1.7	27	25	0.29	0.11	0.02–0.60
1.0–1.4	48	59	0.38	0.23	0.10–0.56	24	22	0.31	0.13	0.02–0.74
1.5–1.9	19	31	0.28	0.49	0.16–1.5	7	13	0.15	0.09	0.01–0.63
≥2.0	20	41	0.20	0.15	0.05–0.44	12	24	0.16	0.06	0.01–0.32
χ^2 for trend			25.7 ($p < 0.001$)					10.3 ($p < 0.001$)		
Height of room (m)										
<2.8†	61	45	1.0	1.0		22	12	1.0	1.0	
2.8–3.1	72	71	0.77	0.91	0.41–2.0	30	26	0.62	0.54	0.09–1.3
≥3.2	91	108	0.65	0.64	0.31–1.3	40	54	0.39	0.23	0.06–0.84
χ^2 for trend			3.5 ($p = 0.06$)					5.5 ($p = 0.02$)		
Floor of apartment										
Ground†	106	92	1.0	1.0		50	32	1.0	1.0	
1	77	78	0.85	0.79	0.40–1.5	23	34	0.30	0.12	0.03–0.46
2–3	27	34	0.66	0.88	0.36–2.1	14	22	0.29	0.11	0.02–0.54
≥4	14	20	0.59	0.62	0.20–1.9	5	4	0.56	0.72	0.07–7.01
χ^2 for trend			3.0 ($p = 0.08$)					5.0 ($p = 0.02$)		

* EOR_1, matched exposure odds ratio; EOR_2, matched logistic exposure odds ratio, adjusted for education, occupation, occupational exposure, history of tuberculosis, chronic bronchitis, family history of cancer, smoking, and living area; CI, confidence interval; EOR_3, matched logistic exposure odds ratio, adjusted for passive smoking in addition to all of the variables listed above.

† Referent.

able on a scale smaller than the district. We knew that separation of the effects of outdoor air pollution from those of indoor air pollution might be difficult. This led us to match on residence as a proxy for matching on outdoor air pollution level. In addition, our results, demonstrating a clear reduction in risk of lung cancer for living in a house with large openings onto the outside, indicate that outdoor air pollution is unlikely to explain or confound the association found between lung cancer risk and indoor sources of air pollution.

Our results showed that comparability between cases and controls with regard to basic demographic variables was good, suggesting that these demographic variables might not have a major confounding effect. Furthermore, education and occupation, which were considered good representative vari-

ables of social class, were also controlled for in the analysis.

Since the number of cases in each histologic category was limited, a separate analysis could not be carried out for the association of indoor air pollution with specific histologic types of lung cancer. Some diagnostic error may also have occurred. However, undifferential misclassification of cases and controls usually leads only to a bias toward the null and cannot explain the observed results.

It is possible that some social class differences between cases and controls could account for part of the difference in ventilation conditions. The finding of a higher risk of lung cancer among subjects living at street level could be explained by a higher concentration of both indoor and outdoor air pollutants on the ground floor as opposed to higher floors, where natural ventilation is usually better. Social class, which is closely linked with housing conditions in China, was nevertheless more strongly associated with the total surface of the living area than was the specific measure of ventilation. Although cases had smaller living areas than controls, the difference was not substantial. After adjustment for education, occupation, and living area, the relation between ventilation conditions and lung cancer risk remained. This means that any bias linked to social status cannot be a major confounder of the observed association. Recall bias can affect most retrospective studies; however, in this study, the size of ventilation openings was objectively measured, so the association between ventilation conditions and lung cancer risk cannot be an artifact of recall bias.

Smoking was the major cause of lung cancer in both sex groups, and a clear dose-response relation was observed between the amount of tobacco smoked and lung cancer risk. High smoking rates were observed in both male and female groups. These rates were higher than those obtained from a case-control study of lung cancer carried out among Shanghai Chinese women (11) but similar to rates from other studies (6, 10, 18, 34). The subjects of this study belonged to an older population and had relatively low social status (a low educational level and the major occupation of worker). These two factors are known to be associated with high smoking rates (35). Furthermore, the definition of a smoker in this study included both ever and current smokers. For instance, if we had counted only current smokers, the smoking rate would have been reduced to 14 percent in female controls. Passive smoking may also account for some excess risk, although increased risk was only observed in the women living with husbands who smoked heavily. No effect was seen for women married to light smokers. This may be explained by the reduced sample size and by the imprecise quantification of passive smoking. The results of other studies in Chinese women have suggested that passive smoking contributes to a slight increase in lung cancer risk (11, 18).

Several reports of environmental monitoring showed that the concentrations of nitrogen oxide, sulfur dioxide, benzo(*a*)-pyrene, and total suspended particulate matter in Guangzhou were higher in dwellings than in the outdoor atmosphere and varied according to time of day and season (36). Three peaks of pollutant concentrations during the day were correlated with cooking activities. Results of studies also showed that there were higher concentrations of suspended dust and suspended benzo(*a*)pyrene in the rooms and urinary benzo(*a*)pyrene in housewives in households where coal was used as a cooking fuel compared with households where petroleum gas was used (36, 37). Results of a study conducted in the north of China showed that use of coal for heating elevated the risk of lung cancer in comparison with use of gas. Cooking in the bedroom was also related to an excess risk (34). High mortality from female lung cancer in Xuan Wei County, Yunnan Province, was also associated with the combustion of smoky coal at home (38). These results indicated that home cooking practices were a major source of indoor air pollutants and that coal produced more severe air pollution than other kinds of domestic fuel.

Evidence also comes from the evaluation

of occupational exposure to coal burning. Steel, gas, and coke oven workers have an elevated risk of lung cancer (39–45). The results of animal experiments have demonstrated that some components of coal fumes are carcinogenic or mutagenic (38, 46, 47). Since coal use, frequent home cooking, and lack of an apparatus for extracting fumes are universal in Guangzhou, it was difficult to find a significant difference between any population groups. However, this indicates that severe indoor air pollution exists for most families in Guangzhou, where people live in comparatively overcrowded conditions with poor ventilation. Better ventilation of houses could thus play a key role in improvement of the indoor microenvironment, and dissimilar ventilation conditions could be responsible for different exposure levels of lung cancer cases and controls. During the study period, there was in most houses no artificial ventilation such as air conditioning, so the indoor microenvironmental conditions depended mainly on natural ventilation. The area of ventilation (as defined by the area of openings to the outside) was a good representative measure of ventilation conditions. This is in agreement with other studies on indoor air pollution showing that the concentrations of pollutants are greatly affected by ventilation (19, 34).

In summary, the results of this study suggest that indoor air pollution produced during home cooking is a risk factor for lung cancer in Guangzhou, especially for women, who are more likely to be exposed to coal fumes and cooking oil vapors in the kitchen. This could contribute to the high rate of lung cancer in Chinese women. Further investigations are needed to clarify the precise nature of indoor air pollutants and their carcinogenic mechanisms. It would also be informative to conduct studies by major histologic type, particularly in Chinese women, among whom adenocarcinoma is unusually frequent. Finally, this study was not designed to evaluate the effect of outdoor air pollution; that must be left to future research. In the meantime, our data indicate that in Guangzhou, there are sources of indoor air pollution which play a role in the occurrence of lung cancer independently of active smoking and outdoor air pollution.

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A Case-Control Study of Childhood and Adolescent Household Passive Smoking and the Risk of Female Lung Cancer.

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To evaluate the risk of female lung cancer from passive smoking (PS), a 1:1 matched case-control study was conducted in Harbin, China. One hundred and fourteen females with primary lung cancer, aged 30 to 69 years, and their hospital-based controls were interviewed using a standard questionnaire. The controls were patients without cancer, from the same hospital as the cases and matched on age (± 5 years), residential area and lifetime smoking habits. Information on PS was collected by each residence for each of the following periods: 0-6, 7-14, 15-22, 23-30 and 31-69 years.

The risk of lung cancer was increased for household exposure under the age of 14 years to maternal smoking (odds ratio, OR=2.70, 95%CI=1.49-4.88), but not for exposure to paternal smoking (OR=1.40, 95%CI=0.79-2.50). The risk was highest in those exposed under the age of seven (OR=3.46 95%CI=1.80-6.65) and was also significant at ages 7-14 (OR=3.06, 95%CI=1.62-5.57) and 15-22 (OR=3.10, 95%CI=1.52-6.31). The OR increased with the amount of passive smoking (P<0.001). These findings suggest that PS, particularly during childhood, increases the risk of female lung cancer and that the assessment of PS should be done by different periods of exposure.

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A Case-Control Study of Idiopathic Pulmonary Fibrosis (IPF).

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This is a multicenter (16 centers) case-control study that examines potential risk factors for IPF, a progressive disease that causes pulmonary interstitial fibrosis. The study currently includes 167 cases and 261 controls; 59% of cases are male and 85% are non-Hispanic white. Median age for cases is 61.5 years. Two controls per case are identified through random digit dialing and matched on gender, age and geographic location. Telephone interviews are conducted to collect information on smoking, occupational exposures, environmental exposures and host factors. Clinical data include pulmonary function tests, X-ray reports and lung biopsy reports. Most referred cases have been interviewed (2% refusal, 5% deceased); refusal rate for controls has been low (9%). Conditional logistic regression was performed on 150 matched sets. Univariate analyses were used to select variables for inclusion in multivariate models. After adjustment for residual age effects in the multivariate model, potential causal factors with odds ratios (95 percent confidence intervals) are: reported occupational asbestos exposure 2.5 (0.95-6.49); reported occupational exposure to vegetable/animal dust 2.7 (0.86-8.27); farming activities 3.0 (1.45-6.10); work in a chemical or petrochemical plant 4.5 (1.23-16.59); cigarette smoking 1.8 (1.05-3.17); and occurrence of pneumonia at least once 1.6 (0.98-2.59). These findings suggest that some cases of IPF may be caused by environmental factors.

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Exposure to biogenic silica fibers and respiratory health in Hawaii sugarcane workers.

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Scientists have theorized that naturally occurring biogenic silica fibers (BSF) could affec workers health in a manner similar to other respirable fibers, such as asbestos. The authors conducted a cross-sectional environmental and medical survey of 355 male Hawaiian sugarcane workers to test this hypothesis. More than 120 personal breathing zone samples were collected to develop a job-exposure matrix and to categorize workers by BSF exposure. Respiratory health data included the prevalence of respiratory symptoms, pulmonary function, and chest radiograph results. The prevalences of respiratory symptoms, chest radiograph findings, and pulmonary function relate conditions did not differ by BSF-exposure category Cigarette smoking was associated with respiratory symptoms and pulmonary obstruction. Fifteen worker had pleural thickening or pleural plaques and 3 of these workers were exposed to BSF for more than te years. BSF exposure does not appear to have influenced the respiratory health of the sugarcane workers studied by the authors.

KEYWORDS: occupation, sugarcane, fibers, pulmonary

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Protection of the Lung From Smoking Damage by Eating Fish.

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High fish consumption is characteristic of the Japanese-American men of the Honolulu Heart Program (HHP). Analyses of data from the ARIC study suggest that a high fish intake protects the lung against smoking damage. Measurements of forced expiratory volume in 1 second (FEV_1) and smoking status in the HHP cohort allow a cross-sectional test of this hypothesis. Among 8006 men 45-68 yrs old in 1965-68, 6346 had acceptable spirograms. Within current smokers, 1545 men consumed fish less than twice a week and 1264 ate twice a week or more. Controlling for cigarettes/day, age, height and daily calorie intake, separate regression models revealed adjusted regression coefficients of -10.1 ml FEV_1 per year of smoking [95% Confidence Interval: -14, -7] at low levels of fish intake, and -4.4 [-8, -0.6] at high levels. The coefficients were significantly different (p=0.003). These differences reflect a predicted FEV_1 103 ml higher in the high fish group at 45 years of smoking, but no difference in FEV_1 at 25 years. Similar analyses for cig/day produced significantly different coefficients (p=0.047) of -4.2 [-6, -2] ml FEV_1 per cig/day for low fish intake and -6.2 [-8, -4] for high intake. These contrasting coefficients appear to contradict the fish protection model, with a larger decrement in FEV_1 per cig/day in the high fish intake group. However, the predicted FEV_1 at 10 cig/day is 53 ml higher in the high fish group, with no difference in FEV_1 noted between groups at 40 cig/day. This feature actually supports the hypothesis, suggesting the protective role of fish is "saturated" at higher "doses" of cigarette smoking. These findings support the hypothesis that frequently eating fish partially protects the lung from smoking damage but that such effects may be lost with heavy smoking.

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Active and Passive Smoking and Pathological Indicators of Lung Cancer Risk in an Autopsy Study

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Objective.—The association between involuntary smoking and lung cancer has been supported by most epidemiologic studies, but a number of authors and interest groups claim that the possibility of bias has not been excluded. Few autopsy-based studies have explored the role of active smoking and other exposures in lung carcinogenesis, and none has been previously done to examine the role of passive smoking. We have undertaken such an autopsy-based study in Athens, Greece.

Design.—Lung specimens were taken at autopsy from 400 persons 35 years of age or older, of both genders, who had died within 4 hours from a cause other than respiratory or cancer in Athens or the surrounding area. For each person at least seven tissue blocks were taken from the main and lobar bronchi and at least five blocks from the parenchyma, including an average of about 20 smaller cartilaginous bronchi and membranous bronchioles. The specimens were examined without knowledge of the exposures of the particular subject in Turin, Italy. For 283 (71%) of the subjects the preservation of the bronchial epithelium was satisfactory for pathological examination, and for 206 among them (73%) an interview could be arranged with their next of kin, focusing on smoking habits of the deceased and their spouses, as well as other variables. The interviewers were not aware of the results of the pathological examinations.

Main Outcome Measure.—Specimens were examined for basal cell hyperplasia, squamous cell metaplasia, cell atypia, and (in membranous bronchioles and bronchiolo-alveolar airways) mucous cell metaplasia, ie, pathological entities that may be lung cancer risk indicators or epithelial, possibly precancerous, lesions (EPPL). The gland and wall thicknesses were also measured and their ratio calculated (Reid Index).

Results.—In comparison with nonsmokers, EPPL values were significantly higher among current smokers and higher, but not significantly so, among former smokers. Furthermore, EPPL values were significantly higher among deceased nonsmoking women married to smokers rather than to nonsmokers. In this set of data neither occupation nor residence was associated with EPPL, but this could be due to the poor correlation of residential history with exposure to air pollution and the lack of adequate standardization of contemporary Greek occupations. The Reid Index was higher among smokers and former smokers in comparison with nonsmokers, among subjects with mainly urban residence in comparison with those with mainly rural residence, and among nonsmoking women married to smokers in comparison with those married to nonsmokers, but none of these differences was statistically significant.

Conclusion.—These results provide support to the body of evidence linking passive smoking to lung cancer, even though they are based on a study methodologically different from those that have previously examined this association.

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THE ASSOCIATION between exposure to environmental tobacco smoke and lung cancer, first reported in 1981,[1,2] has been supported by the collective evidence of several epidemiologic studies.[3-11] However, some authors[12,13] and a number of special interest groups[14] have challenged the epidemiologic findings, invoking the operation of unlikely but conceivable biases. To further examine the etiologic importance of involuntary smoking in lung carcinogenesis, we have undertaken an autopsy-based epidemiologic study in Athens, Greece. Lung specimens were examined without knowledge of the exposures of the particular subject for pathological entities that are considered lung cancer risk indicators, and the findings were correlated with independently elicited exposure information concerning the deceased and provided by his or her next of kin.[15] Several of the pathology-based studies[16-31] have examined the importance of tobacco smoking and various correlates of air pollution as risk factors of pathoanatomic indicators of lung cancer, chronic bronchitis, or respiratory performance, but there have been no previous such investigations of the role of involuntary smoking.

METHODS

Autopsies are mandatory in Greece when a death is due to external causes or has occurred within 24 hours after the development of symptoms and the patient has not been under the regular attendance of a physician who is willing to sign the death certificate. During a 4-year period (September 1986 through October 1990) about 12 000 autopsies were performed in the Coroner's Center of Athens, the major of two centers that cover the 4 million–large population of Attica. During this period one of us (E.A.), a pathologist specifically trained in the Turin center and collaborating with the Coroner's Center of Athens, obtained lung specimens from 400 persons 35 years of age or older, of both genders, who had

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Table 1.—Distribution of the Initially Selected 400 Subjects (A), the 283 Subjects for Whom Suitable Samples Were Taken (B), and the 206 Persons for Whom Both Suitable Samples and Interviews Were Available (C), by Cause of Death, Age, and Gender.

	Group		
	A No. (%)	B No. (%)	C No. (%)
Cause of death			
Coronary heart disease	234 (59)	170 (60)	139 (68)
Other cardiovascular diseases	42 (10)	32 (12)	20 (10)
Diseases of the digestive system	25 (6)	17 (6)	10 (5)
Diseases of the genitourinary system	4 (1)	4 (1)	3 (1)
Accidents and other external causes	58 (15)	46 (16)	34 (16)
Unknown (but nonrespiratory)	37 (9)	14 (5)	...
Age, y			
≤39	4 (1)	4 (1)	4 (2)
40-49	35 (9)	25 (9)	18 (9)
50-59	74 (19)	56 (20)	39 (19)
60-69	89 (22)	66 (23)	51 (25)
70+	173 (43)	121 (43)	94 (45)
Unknown	25 (6)	11 (4)	...
Gender			
M	275 (69)	203 (72)	144 (70)
F	117 (29)	80 (28)	62 (30)
Unknown	8 (2)	...	...

died within the last 4 hours from a cause other than respiratory or cancer. Specimens were collected when the indicated pathologist was on duty during the early morning hours at the Coroner's Center of Athens, and the 400 specimens were all that were available to him during his service at the time period of the study. The subjects were of Greek nationality and all died in the Attica area (which includes Greater Athens) but could have been current or past residents of any area of Greece. The pathological examinations were undertaken in Turin by two pathologists (F.M., L.D.) who were blinded about the identity of the subject and his or her past exposures.

For each subject, at least seven tissue blocks were taken from the main and lobar bronchi and at least five blocks from the parenchyma (one for each lobe), including an average of about 20 smaller cartilaginous bronchi and membranous bronchioles; additional blocks were obtained from scars and areas of fibrosis, when present. At least two histological sections were examined from each block.

In 283 (71%) of the subjects the preservation of the bronchial epithelium was satisfactory according to the criteria set by Auerbach et al,[17] and only these cases were considered suitable for further study. In these subjects several morphological features were examined to assess the precancerous potential in the bronchial tree.[16,17,20,21,24]

Basal cell hyperplasia, squamous cell metaplasia, and cell atypia were considered as lung cancer risk indicators or epithelial, possibly precancerous, lesions (EPPL) in main plus lobar and in other cartilaginous bronchi, whereas in membranous bronchioles and bronchiolo-alveolar airways, mucous cell metaplasia was also taken into account (14 variables). For each of these 14 variables several observations were available for every study subject. When absent EPPLs were graded as 0, or as 1 to 3 (1 to 4 for atypia) when present. The criteria for the scoring were based on the degree of changes for hyperplasia and atypia, and on the extension of changes around the airway circumference for squamous and mucous metaplasia. A set of photographic reference standards was prepared and used for comparison during examination and grading. Each slide was examined by the two pathologists and discussed when the grade scores were not in agreement.

The sum of the grade scores assessed for each of the 14 EPPL variables was calculated and expressed as a percentage of the maximum sum that could be obtained. Thus, for basal cell hyperplasia in main plus lobar bronchi, there were usually seven observations for every study subject (two for the main and five for the lobar bronchi). Each observation was assigned a grade from 0 to 3 (basal cell hyperplasia from absent to maximum), with a grade sum ranging from 0 to 21. If the actual grade sum were 7, its percentage expression of the maximum grade sum would be 33. The resulting percentage values of the 14 variables were then added. This method, introduced by Wright et al[22] in a morphological grading of bronchiolar lesions, allows the estimation of a total EPPL grade score. As Wright et al[22] have pointed out, this procedure usually generates a variant of the mean of all the grades, although in this instance, the method assigns equal weights to atypia (original scale from 0 to 4) and to hyperplasia or metaplasia (original scales from 0 to 3). The total EPPL grade score has a positively skewed distribution; most values lie between 10 and 80, with occasional values above 100.

Independently, the Reid Index (RI) was also determined for every study subject.[15] This index reflects bronchial mucous gland enlargement and has been regarded by several workers[22,23] as a morphologic counterpart of chronic bronchitis. The RI is calculated[18] as the ratio of the thickness of the bronchial mucous glands (G) to the bronchial wall (W) thickness (inner perichondrium to basement membrane), and is usually graded as 1 ($G/W \leq 0.35$), 2 ($0.35 < G/W \leq 0.50$), or 3 ($G/W > 0.50$). The index was evaluated in the two main bronchi and five lobar bronchi of each subject, and the mean value for this subject was then estimated.

An effort was made to identify the next of kin of the deceased. The interviewers, both medical doctors (X.Z., A.K.), explained by telephone or, more frequently, through an assistant the purpose of the study, and requested permission to visit and administer an interview in person. The interviewers were not aware of the results of the pathological examinations, which were performed without knowledge of the exposures of the particular subject. For 206 subjects an interview was done, whereas for the remaining 77 (27%) there was either refusal (48 persons) or loss of contact (29 persons). The interviewed persons were spouses (43%), children (19%), brothers or sisters (6%), other relatives (6%), or others (26%).

Table 1 shows distributions by diagnosis, age, and gender of the initially selected 400 subjects, the 283 persons for whom suitable samples were taken, and the 206 persons for whom both suitable samples and interviews were available.

The interviews were done with standardized questionnaires. Data concerning demographic characteristics were obtained, and information concerning occupation, residential history, and smoking habits of the deceased and his or her spouse was recorded. Specifically, the next of kin was asked to indicate, among other things, the employment history of the deceased; whether he or she was a smoker or an ex-smoker at the time of death and, if so, what was the average number of cigarettes per day; and where he or she has lived and for how long. For every married subject, smoking information about the spouse was also recorded.

Standard regression procedures were used for the analysis. The values for EPPL and RI were alternatively used as dependent variables. Independent variables were, in addition to gender, age and years of schooling of the deceased, resi-

Table 2.—Cross-Classification of 206 Subjects by Reid Index (RI) and Total Score of Epithelial, Possibly Precancerous, Lesions (EPPL) in the Bronchial Tree

RI	EPPL 0-19	20-39	40-59	60-79	80+	Total
0.0-1.4	12	3	1	2	3	21
1.5-1.9	9	5	4	1	1	20
2.0-2.4	20	11	15	11	9	66
2.5-2.9	8	19	19	13	14	73
3.0	3	5	5	3	10	26
Total	52	43	44	30	37	206

dential history, and smoking habits. Specifically, the subjects were classified into those who lived most of their lives in urban areas (population of ≥100 000) and those who lived most of their lives in rural areas. With respect to smoking habits, current smoking and past smoking were introduced into the model as indicator variables, whereas the effect, if any, of the daily amount of cigarettes, among smokers and past smokers separately, was assessed by entering the appropriate terms in the model to restrict information to the relevant groups. Occupation of the deceased was also evaluated in the initial models using five indicator variables for professionals, urban blue-collar workers, agricultural workers, self-employed plus commercial workers, employees, and housekeepers.

RESULTS

Table 2 shows the cross-classification of the 206 subjects by EPPL and RI values. There is a fair degree of correlation (the correlation coefficient, based on individual pairs of observations, is +0.40), which is statistically significant ($P<.001$). Table 3 presents univariate distributions of these subjects by age, gender, years of schooling, most recent occupation, residential history, and smoking habits. This table also shows mean values and corresponding standard errors of EPPL by group. Due to intercorrelations among the various independent variables, the EPPL data in Table 3 are not directly interpretable.

Table 4 shows the results of multiple regression analysis using EPPL as a dependent variable and age, gender, smoking habits, and residential history as independent variables. Entering years of schooling and/or occupational groups into the model did not noticeably affect the regression coefficients, nor was there a substantial, significant, or suggestive association of EPPL with any of the occupational groups or with years of schooling. The values for EPPL were substantially and significantly higher among current smokers and higher, but not significantly so, among past smokers. There were no dose-response trends among current or past smokers. With the tobacco smoking terms in the model, EPPL values were significantly higher among female subjects, and there was a nonsignificant decrease with age. Residential history, which is a very crude indicator of long-term exposure to air pollution, was not associated with EPPL. Carcinoma was found in four elderly men (68 to 82 years) who were all heavy smokers (30 to 45 cigarettes per day). Their individual EPPL values were 29, 53, 142, and 253, with the mean equal to 119.

Among the 62 female subjects there were 41 nonsmokers. Among them 17 were married to husbands who were ever smokers, whereas 13 were married to never smokers (for 11 relevant information was not available). Nonsmoking women exposed to environmental tobacco smoke through their husbands had a significantly higher mean value of EPPL, although the estimates were not very precise. Thus, the difference (with the 95% confidence interval [CI]) was 27.88 (5.64 to 50.13), with a two-tailed P of .02. Adjustment for one or more of the other variables indicated in Tables 3 and 4 had no effect.

With respect to RI, no difference or association in the multiple regression analysis was significant at a nominal level ($P<.05$), although the results were, in general, in "expected" directions. Thus, compared with nonsmokers, RI was higher among smokers (difference, 0.125; CI, −0.090 to 0.340) and, to a lesser extent, among past smokers (difference, 0.050; CI, −0.210 to 0.310). The index was also higher among those with mainly urban residence (difference, 0.177; CI, −0.030 to 0.384) and among nonsmoking women married to smokers rather than to nonsmokers (difference, 0.220; CI, −0.149 to 0.589).

COMMENT

Studies linking pathoanatomic findings in the lungs with data concerning exposures to tobacco smoking and air pollution have concentrated on lesions thought to be risk indicators of lung cancer,[14,17,22-24] on pathological abnormalities associated with functional respiratory changes,[22-24] or on pathological changes linked to the clinical syndrome of chronic bronchitis.[18,22-25,29] The index proposed by Reid[18] as a morphologic correlate of bronchial mucus hypersecretion and, accordingly, chronic bronchitis[18,22] has been associated in some studies with tobacco smoking,[22-25,29] but there are no reports linking RI with air pollution or a proxy variable like residential history. In the present study no significant association was evident between the RI, on the one hand, and any of the exposure variables on the other, although the results were, overall, in expected directions, the index being higher among smokers and urban residents. This may imply that RI, as measured, is not a sufficiently sensitive indicator of the pathological changes associated with chronic bronchitis, or that the unavoidable nondifferential misclassification in exposure ascertainment led to attenuation of weak true associations. Nevertheless, the moderately strong and highly statistically significant association between RI and EPPL suggests that there are common factors in their etiology (although not necessarily with equally strong etiologic relations), and that the reliability of these measurements is not much lower than that of many other variables used in epidemiologic studies (for which the correlation coefficients vs their own standards are frequently between 0.5 and 0.6).

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Table 3.—Univariate Characteristics of the 206 Studied Subjects and Mean Values of Epithelial, Possibly Precancerous, Lesions (EPPL), by Group

Variable	No.* (%)	EPPL (SE)
Age, y		
35-49	22 (11)	67.45 (11.69)
50-59	39 (19)	56.74 (7.56)
60-69	51 (25)	48.86 (5.80)
70-79	63 (30)	38.92 (3.99)
80-89	28 (14)	48.26 (7.48)
90+	3 (1)	42.33 (27.51)
Gender		
M	144 (70)	47.82 (3.30)
F	62 (30)	52.19 (5.95)
Schooling, y		
0	15 (8)	46.40 (10.65)
1-6	96 (47)	51.22 (4.58)
7+	92 (45)	47.17 (5.78)
Occupational activity		
Professionals	5 (2)	70.40 (21.72)
Commercial, etc	20 (10)	40.15 (5.96)
Employees	53 (27)	42.53 (3.79)
Manual workers	72 (36)	55.18 (6.23)
Agricultural	14 (7)	54.00 (13.15)
Housekeeping	36 (18)	41.22 (5.84)
Residential history		
Mainly urban	152 (77)	49.88 (3.44)
Mainly rural	45 (23)	49.42 (6.37)
Smoking habits		
Nonsmokers	62 (31)	41.26 (5.61)
Ex-smokers		
1-20 cigarettes/d	19 (10)	45.37 (11.10)
21-40 cigarettes/d	9 (5)	31.78 (6.82)
41+ cigarettes/d	8 (4)	42.88 (9.09)
Current smokers		
1-20 cigarettes/d	51 (25)	58.92 (5.74)
21-40 cigarettes/d	37 (19)	61.43 (7.53)
41+ cigarettes/d	14 (7)	42.93 (6.54)

*There are missing values: years of schooling, three; occupational activity, six; residential history, nine; smoking habits, six.

Table 4.—Multiple Regression-Derived Regression Coefficients of Epithelial, Possibly Precancerous, Lesions on a Number of Independent Variables: Point Estimates, 95% Confidence Intervals, and Two-Tailed P Values*

Variable	Category	Regression Coefficient (95% CI)	Unit of Independent Variable	P (Two-Tailed)
Age	Continuous	−4.65 (−9.85 to 0.54)	10 y	.08
Gender	Male	Baseline		
	Female	17.10 (1.77 to 32.43)	NA	.03
Smoking habits	Nonsmokers	Baseline		
	Current smokers	23.52 (7.57 to 39.47)	NA	.04
	No. of cigarettes	−2.69 (−8.04 to 2.66)	10 cigarettes	.32
	Ex-smokers	7.39 (−11.95 to 26.73)	NA	.45
	No. of cigarettes	−0.32 (−7.73 to 7.09)	10 cigarettes	.93
Residential history	Mainly rural	Baseline		
	Mainly urban	−4.89 (−20.25 to 10.47)	NA	.53

*CI indicates confidence interval; and NA, not available.

approach of the present study drew heavily from the studies done by Auerbach and colleagues[16,17,20,21,24] over a period of 30 years. These pioneering studies are of great relevance in evaluating pathological lesions, although it is possible that minor biases may have been introduced in their sampling procedures; furthermore, there has not been a complete consensus on the relative value of the early lesions as predictors of the future occurrence of tumors.[24] We have also used the semiquantitative scoring system that was introduced by Wright and her colleagues,[22] a system that imparts an element of objectivity to the summarization of the pathological findings.

Auerbach and colleagues[16] postulated that there should be changes in the bronchial epithelium of patients with lung cancer, as well as in smokers, that differ markedly from those in nonsmokers. They have focused on four types of epithelial changes (basal cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ) and found that these changes (mainly cells with atypical nuclei) were much more common in smokers (particularly heavy smokers), whereas among past smokers the findings were minimal and, among nonsmokers, urban residence had little and age and gender virtually no effect (if anything, older women had fewer changes).[17,20,21] In a later study, Auerbach et al[24] have shown that smoking of low tar and nicotine cigarettes generates substantially fewer histological changes in the bronchial epithelium. The results of the Auerbach studies do not necessarily imply that all the indicated epithelial lesions represent stages of a unidirectional carcinogenic process; indeed, the findings of other studies[13,25] suggest that some of the detectable epithelial lesions are likely to be correlates rather than intermediate steps in lung carcinogenesis.

With respect to demographic variables (broad occupational categories, age, and gender), the results of the present study are compatible with earlier reports. After controlling for tobacco smoking, women had higher EPPL values and there was a slight negative association of EPPL with age, in line with the findings reported by Auerbach et al.[20] Also, broad occupational categories are not expected to show substantial variability in lung cancer risk, even though particular occupations have definitely been shown to be at increased risk. Furthermore, categorization of occupations is not adequately standardized in Greece, and the lack of association between occupation and lung pathology may be due to inadequate information on occupation.

There were substantially and significantly higher EPPL values among smokers and higher, but not significantly so, EPPL values among past smokers. The lack of dose-response patterns is not surprising. Next of kin responders frequently remember whether the deceased was a smoker, but it is rather unusual for them to have accurate knowledge of the number of cigarettes smoked daily. The resulting nondifferential misclassification is likely to attenuate any existing dose-response pattern to the point of nondetectability in studies of moderate size. It is also possible that heavy smokers with extensive pathological lesions in the lung become symptomatic and thus less likely to be included among those who would be autopsied after their death; a similar selection with respect to passive smokers is implausible, since very few, if any, among them would have such extensive pathological lesions.

The finding concerning passive smoking is statistically significant and adds to the substantial body of evidence linking exposure to environmental tobacco smoke with lung cancer.[3-11] Although the examined subjects represent a selected sample, there is no likely selection factor that could affect the joint distribution of any of the exposure variables and EPPL (over and beyond their actual associations), since all EPPL and RI assessments were done blindly in a different center. Furthermore, selective recollection and other types of biases that have been invoked by some authors[2,3] to explain, in noncausal terms, the association of passive smoking with lung cancer are either nonapplicable or highly unlikely in the context of an autopsy-based study.

The apparent effect of passive smoking may seem too large in comparison to the effect of active smoking in this investigation. Thus, the odds ratio for an EPPL score of 60 or more contrasted to an EPPL score of less than 40 was 0.9 for mainly urban residents (compared with mainly rural residents), 1.4 for former smokers (compared with nonsmokers), and 4.4 for active smokers (compared with nonsmokers), whereas among nonsmoking women the odds ratio was 6.0 for those married to smokers (compared with those married to nonsmokers). The corresponding odds ratios for an RI of 2.5 or higher contrasted to an RI of less than 2.0 were 1.5, 1.7, 2.4, and 1.3. However, EPPL and RI differences and the odds ratios describing the effects of active and passive smoking are not directly comparable. Active smokers are compared with nonsmokers, whether these were exposed or nonexposed to the passive smoking indicator (husband's smoking), whereas passive smokers are compared with subjects unexposed to the passive smoking indicator. It has been pointed out by Vutuc[26] and others[2,7] that whenever the proportion of nonsmokers who are passive smokers is large (as in the present study or in any setting in which a large majority of men but only a small minority of women are smokers) and the impact of passive smoking is modest or substantial, the effect of active smoking can be grossly underestimated. In the present study, changing the reference group from "nonsmokers" to "nonsmokers unexposed to the passive smoking indicator" would increase the odds ratio for active smoking to almost 10 (with reduced precision, since there would be few subjects in this new reference group). Other factors must also be taken into account. Confidence intervals for passive smokers are fairly large, and they could easily accommodate predicted ratios of effects of active and passive smoking. In addition, the information concerning active smoking of the deceased was obtained from proxy sources, whereas information concerning passive smoking was obtained, in many instances, from individuals who were themselves the sources of this exposure for the deceased. In the former situation nondifferential misclassification is more extensive than in the latter, and the resulting effect

attenuation is correspondingly larger. Moreover, many smokers, even in Greece, have switched to low tar and nicotine cigarettes, and this should be expected to modify the effects of active smoking[24] while having little, if any, impact on the concentration and composition of environmental tobacco smoke (low tar and nicotine cigarettes are made so by the filter rather than by the composition of tobacco). Last, there is other evidence[27,28] that exposure to environmental tobacco smoke could be more injurious to health than it would be predicted to be on the basis of cotinine excretion studies.

The present data cannot substantiate or challenge the notion that air pollution, of the type and levels present in Athens, is an important determinant of EPPL and, inferentially, lung cancer. Ascertainment of exposure to air pollution on the basis of the residential history, as elicited through a proxy interview, is probably inadequate; furthermore, EPPL is a composite index, some of the components of which may be weak or no predictors of lung cancer risk, thus reducing the overall sensitivity and predictive power of EPPL. Overall, the results of the present investigation do not deviate from the "negative" evidence generated by other pathology-focused studies that have attempted to examine the effect of general air pollution on lung cancer risk,[20] and cannot facilitate the resolution of this important and controversial issue.[39-51]

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A BRIEF ORIGINAL CONTRIBUTION

Passive Smoking and Canine Lung Cancer Risk

John S. Reif,[1] Kari Dunn,[2] Gregory K. Ogilvie,[3] and Cheryl K. Harris[2]

A case-control study was conducted to determine whether household exposure to environmental tobacco smoke is associated with an increased risk for lung cancer in pet dogs. Lung cancer cases and controls with other forms of cancer were obtained from two veterinary teaching hospitals during 1985–1987. Exposures assessed included the number of smokers in the household, the amount smoked, and the proportion of time spent indoors by the pet. A weak relation was found for exposure to a smoker in the home (odds ratio = 1.6, 95% confidence interval 0.7–3.7), after controlling for confounding in stratified analyses. Strong evidence for a further increase in risk associated with more than one smoker in the home was not found, nor was a significant trend observed for increasing number of packs of cigarettes smoked per day or an exposure index based on number of smokers in each household, packs smoked per day, and the proportion of time the dog spent within the home. However, skull shape appeared to exert effect modification; the risk was restricted to breeds with short and medium length noses (odds ratio = 2.4, 95% confidence interval 0.7–7.8). Despite the inconclusive findings of the current study, epidemiologic studies in pet animals may add to our understanding of environmental tobacco smoke effects in human populations. *Am J Epidemiol* 1992;135:234–9.

dogs; lung neoplasms; tobacco smoke pollution

Spontaneous canine neoplasms may provide useful models for studying the health effects of environmental hazards. Many forms of canine cancer resemble their human analogs in biologic behavior, pathologic expression, and recognized risk factors. Dogs share the environment intimately with humans, and thus they may constitute a "sentinel" species for human disease. Epidemiologic studies of environmental risk factors for cancer in pet dogs have been advocated because of the relative freedom from confounding factors such as occupational exposures and the dog's shorter life span and restricted residential mobility (1).

The relation between exposure to environmental tobacco smoke and the risk of human lung cancer and other, nonneoplastic respiratory diseases has received intense scrutiny from the scientific community, health policymakers, and others (2–6). The current study was designed to test the hypothesis that exposure to environmental tobacco smoke in the home constitutes a risk factor for lung cancer in dogs.

MATERIALS AND METHODS

All confirmed cases of canine lung cancer (n = 70) for the years 1985–1987 were se-

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Abbreviation: CI, confidence interval.

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lected from the oncology records systems of two university veterinary teaching hospitals (the University of Illinois and Colorado State University). Unmatched controls (n = 106) with other forms of cancer not suspected of being related to cigarette smoking in humans were selected randomly from the oncology data bases of the same institutions for the same years, yielding a case:control ratio of 1:1.5. The diagnoses of the primary lung cancer cases and cancer controls were verified histologically.

A letter soliciting participation was mailed to the household of each subject, with instructions to complete and return a questionnaire. Demographic information was collected for each participant. Exposures assessed among cases and controls included the number of smokers who resided in the household, the number of packs of cigarettes smoked per day by the heaviest smoker, and the proportion of time (per 24-hour day) spent by the dog inside the home. An exposure index was created for each subject by multiplying the number of smokers in each household by the number of packs smoked per day by the proportion of time the dog spent within the home. Thus, subjects that lived in homes where there was no resident smoker were assumed to have received no exposure.

Odds ratios with approximate 95 percent confidence intervals (7) were calculated to estimate risk. Mantel-Haenszel stratified analyses were used to control for confounding (8). The Mantel extension chi-square test was used to evaluate trends across strata of increasing dose (9).

Age, sex, hospital, proportion of the day spent indoors, body size, and skull shape were evaluated for confounding or effect modification. Body size (ideal weight for breed) could have influenced proximity to a smoking owner, as has been suggested for other human-canine exposures (10). It has been suggested that skull shape influences risk for respiratory cancer; long-nosed breeds have been shown to be at excess risk for nasal cancer in some studies (11, 12) but not in others (13). The suggestion that long nosed (dolichocephalic) breeds may more effectively filter and remove airborne particulates and carcinogens stimulated the inclusion of skull shape in stratified analyses.

RESULTS

The response rates were 73 percent for cases and 78 percent for controls, yielding final sample sizes of 51 and 83, respectively. Hospital A contributed 55 percent of the subjects—53 percent of the cases and 57 percent of the controls. Smoking was more prevalent among owners of dogs from hospital B, and therefore hospital was included as a potential confounder in all stratified analyses. The demographic and anatomic characteristics of lung cancer cases and other cancer controls were similar (table 1). The relative frequencies of various diagnoses among control dogs (table 2) were representative of all dogs with cancer as reported in other studies of university veterinary hospital populations (14).

A weak association was found between exposure to environmental tobacco smoke and the risk of canine lung cancer. The crude odds ratio for exposure to environmental smoke was 1.5 (95 percent confidence interval (CI) 0.7–3.0). After adjustment for age, sex, skull shape, time spent indoors, and hospital, the odds ratio rose slightly to 1.6

TABLE 1. Selected characteristics of case and control dogs from two veterinary medical teaching hospitals (the University of Illinois and Colorado State University), 1985–1987

Characteristic	Cases	Controls
No.	51	83
Mean age (years)	10.4	10.0
% male	47.1	50.6
Size (pounds)*		
Small (<25)	25.5	19.3
Medium (25–50)	35.3	41.0
Large (>50)	39.2	39.8
Skull shape		
Brachycephalic	5.9	6.0
Mesocephalic	47.1	49.4
Dolichocephalic	47.1	44.6

* To convert pounds to kilograms, multiply by 454 and divide by 1,000.

(95 percent CI 0.7–3.7) (table 3). Effect modification by age appeared to be present; the risk estimate for dogs aged 10 years or less was 2.7 (95 percent CI 1.0–7.2), while that for older dogs was 0.8 (95 percent CI 0.3–2.2).

Evidence of a dose-response relation for passive smoke exposure was largely lacking (table 3). The risk estimate for more than one smoker in the home did not increase substantially over that found with a single smoker. Although the adjusted odds ratios for number of packs of cigarettes smoked daily by the heaviest smoker were in the anticipated direction for a dose response, the trend was not significant ($p = 0.20$). However, the total number of packs smoked in the home by all resident smokers could not be estimated from the data collected. When we evaluated an index of exposure that was calculated by multiplying number of smokers in the home, packs per day smoked by the heaviest smoker, and proportion of the day spent in the home by the dog, no in-

TABLE 2. Classification, by major diagnostic category, of control dogs from two veterinary medical teaching hospitals (the University of Illinois and Colorado State University), 1985–1987

Cancer site or type	No.	%
Breast	10	12.1
Soft tissue sarcoma	13	15.7
Skin and connective tissue	24	28.9
Gastrointestinal tract	9	10.8
Thyroid	5	6.0
Bone	6	7.2
Lymphoid	3	3.6
Other	13	15.7
Total	83	100.0

TABLE 3. Risk estimates for canine lung cancer by exposure to environmental tobacco smoke, University of Illinois and Colorado State University, 1985–1987

Risk factor	Cases exposed (n = 51)	Controls exposed (n = 83)	OR*, †	95% CI*
Presence of smoker in the home				
No smokers	27	52	1.0	
At least one smoker	24	31	1.6	0.7–3.7
No. of smokers in the home				
0	27	52	1.0	
1	16	17	1.6	0.6–4.1
≥2	8	14	1.8	0.4–7.1
	(χ^2 for trend = 0.398; p = 0.53)			
Packs/day‡				
0	27	52	1.0	
<2	15	22	1.2	0.5–3.2
≥2	9	9	3.4	0.7–16.5
	(χ^2 for trend = 1.655; p = 0.20)			
Exposure index§				
0	27	52	1.0‖	
0.25–2.0	16	14	1.9‖	0.8–4.5
>2.0	8	17	0.9‖	0.3–2.9
	(χ^2 for trend = 0.123; p = 0.73)			

* OR, odds ratio; CI, confidence interval.
† Odds ratios were adjusted for age, sex, hospital, skull shape, and time spent indoors.
‡ No. of packs of cigarettes smoked per day by heaviest smoker.
§ No. of smokers × packs/day × percentage of time spent indoors.
‖ Not adjusted for time spent indoors.

crease in risk was seen with presumed increases in exposure to environmental tobacco smoke (table 3).

Skull shape was found to exert a modifying effect on estimated lung cancer risk (table 4). The increase in risk for having a smoker in the home was restricted to members of breeds with short (brachycephalic) and medium length (mesocephalic) noses (odds ratio = 2.4, 95 percent CI 0.7–7.8), while no increase in risk was found in dogs with long noses. However, evidence of a dose-response relation was not found in the brachycephalic-mesocephalic group.

DISCUSSION

Primary canine lung cancer is a rare disorder, in terms of both proportional cancer mortality and prevalence. A prevalence ratio of 4.2 cases per 100,000 dogs was found in one population-based study (15). Lung cancers in dogs are primarily adenocarcinomas of bronchiolar and bronchioloalveolar origin which arise in the peripheral portions of the lung rather than in large airways (16).

Previous interest in canine lung diseases as models for human health effects has focused on the possible role of air pollution in chronic pulmonary disease (17) and in lung cancer (11). When the role of urban residence (a surrogate for air pollution exposure) was tested for its effect on the risk of canine pulmonary or nasal neoplasia, no relation was found (11). Environmental exposures to cigarette smoke were not considered in these analyses; an association between passive smoking and human lung cancer was not described until a decade later. In a recent epidemiologic study of bladder cancer in dogs, no association with exposure to environmental tobacco smoke was found (18).

The increase in risk found in this study in dogs corresponds reasonably well with the estimate of an increased risk for lung cancer

TABLE 4. Risk estimates for canine lung cancer by exposure to environmental tobacco smoke and by skull shape, University of Illinois and Colorado State University, 1985–1987

Risk factor	Brachycephalic/mesocephalic dogs				Dolichocephalic dogs			
	Cases exposed (n = 27)	Controls exposed (n = 46)	OR*, †	95% CI*	Cases exposed (n = 24)	Controls exposed (n = 37)	OR†	95% CI
Presence of smoker in the home								
No smokers	12	29	1.0		15	23	1.0	
At least one smoker	15	17	2.4	0.7–7.8	9	14	0.9	0.3–2.9
No. of smokers in the home								
0	12	29	1.0		15	23	1.0	
1	9	9	3.4	0.8–15.0	7	8	0.8	0.2–3.2
≥2	6	8	1.9	0.4–9.3	2	6	0.6	0.1–6.2
Packs/day‡								
0	12	29	1.0		15	23	1.0	
<2	10	11	2.5	0.6–10.0	5	11	0.7	0.2–2.5
≥2	5	6	2.4	0.4–13.1	4	3	2.1	0.2–25.3
Exposure index§								
0	12	29	1.0‖		15	23	1.0‖	
0.25–2.0	11	6	7.6‖	1.6–35.8	5	8	0.7‖	0.2–2.4
>2.0	4	11	1.2‖	0.2–5.4	4	6	0.6‖	0.1–4.0

* OR, odds ratio; CI, confidence interval.
† Odds ratios were adjusted for age, sex, hospital, and time spent indoors.
‡ No. of packs of cigarettes smoked per day by heaviest smoker.
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in humans of 1.35 that was calculated in a meta-analysis of the first 13 studies of lung cancer risk and passive smoking conducted worldwide (19). The current study suffers from some of the same limitations found in the studies done in humans, i.e, small sample sizes, imprecise risk estimates, and difficulties in measuring exposure.

Risk estimates in this study were stratified according to skull shape, because long-nosed breeds have been found to be at increased risk for nasal cancer in several epidemiologic studies (11, 12) and clinical reports (20). The suggestion that the increased risk of nasal cancer among dolichocephalic breeds may be due to enhanced filtration of airborne particulates and carcinogens led us to examine the relation between skull shape and lung cancer risk. The finding that increased canine lung cancer risk is restricted to dogs with short and medium length noses (brachycephalic and mesocephalic breeds) is consistent with the hypothesis that the relatively efficient air filtration of the long-nosed breeds may exert a protective effect for lung cancer. Experimental attempts to induce lung cancer in dogs by exposing them to cigarette smoke proved successful when the nasal filtration mechanism was bypassed by exposing the animals through a tracheostomy (21). Over 40 percent of dogs that "smoked" unfiltered cigarettes for up to 2½ years developed lesions classified as invasive bronchioloalveolar tumors (21). Furthermore, the low incidence of lung cancer in dogs may be partly attributable to effective filtration of inspired air within the nasal cavity and turbinates.

Use of the dog model has several advantages over comparable studies in humans in that exposures are largely restricted to the home, and potential confounding by occupational exposures to other airborne carcinogens is reduced. Nonetheless, while the dog's mobility is restricted, that of its smoking owner(s) is not, and it becomes difficult to ascertain exposure precisely. In the current study, the proportion of total smoking conducted in the home (as opposed to other sites) was not determined, and information on number of packs currently smoked per day was collected only for the heaviest smoker in the home. Duration of exposure was not evaluated, although it may also be relevant, since the induction time for lung cancer is likely to be measured in years. Thus, misclassification with respect to dose undoubtedly occurred and may have obscured differences between exposure groups. Recent studies in humans have emphasized the importance of childhood and adolescent exposures to environmental tobacco smoke in the household as determinants of the risk of lung cancer (6).

Hospital-based case-control studies may suffer from selection bias. However, in this study, there is no reason to suspect differential referral patterns from smoking and nonsmoking families, and cancer controls were chosen to minimize this possibility. Furthermore, the selection of cancer controls was intended to reduce the information bias that may result from differential recall of exposure among owners of case and control dogs (22).

The rarity of lung cancer in dogs makes a collaborative multicenter case control study the design of choice for further studies of canine lung cancer. Studies of nasal cancer, a more common form of cancer in dogs, are under way to examine the effects of environmental tobacco smoke on the nasal epithelium. Demonstration of an association between exposure to environmental tobacco smoke and canine respiratory cancer would provide additional evidence with which to evaluate this important public health concern.

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ABSTRACTS

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404 PRECURSORS OF CARDIOVASCULAR DISEASE IN A RURAL COMMUNITY - A CROSS - SECTIONAL STUDY.

A.M. Beltran, Jr., M.D., E.I. Cabral, M.D.
Clinical Epidemiology Unit, University of the Philippines, Manila Philippines, with R.F. Heller, M.D. University of NewCastle, Australia.

The Philippines is experiencing an increasing number of cases of ischemic heart disease and hypertension. Since there is a strong association between the presence of risk factors and development of heart disease, this study was conducted to evaluate the extent of high blood pressure, smoking and serum cholesterol level in a sample population living in a rural community of Pila, Laguna.

A random sample of 300 males aged 30 to 70 years drawn from a household register of 2 villages were studied. A validated questionnaire was used to evaluate the presence or absence of these risk factors. The results were: $\bar{x}$ age 45 ± 10 (33-67 yrs)., $\bar{x}$ weight 50 ± 10 (37-93 kg) and $\bar{x}$ height 162 ± 5 (148-181 cm). Their mean systolic blood pressure (SBP) was 132 ± 22 (78-230 mmHg) and mean diastolic pressure (DBP) was 80 ± 12 (54-126 mmHg). Seventy two (24%) were told of having a raised blood pressure but only 34 (11%) were truly hypertensive (SBP > 160 and/or DBP > 95). Fifty seven (19%) had been on drug treatment at one time. One hundred seventy nine (60%) were smokers averaging 14 ± 8 sticks/day (1-40) and began smoking at a mean age of 18 ± 5 (10-40 yrs). The mean serum cholesterol was 4.5 ± 2 (2.2-8.9 mmol) in which 8 (2.6%) had hypercholesterolemia (> 7.0 mmol).

In conclusion, in a rural Philippine community the most prevalent risk factor of cardiovascular disease is smoking. Hypertension is a moderately prevalent condition and high serum cholesterol level does not seem to be a significant risk factor. Therefore, the major thrust in the prevention of heart disease in this community should be the control of smoking.

405 AN APPRAISAL OF INTEGRATED MOTHER AND CHILD HEALTH INTERVENTION PROGRAMME IN RURAL AREA OF RAJASTHAN

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A five year Integrated Mother and Child Health (MCH) Intervention Programme, with support of Indian Council of Medical Research (ICMR), is being implemented in rural block PHC area of Rajasthan State, covering 120,000 population. The Intervention Programme, based on risk approach, aims at 1) improving voverage, quality and utilization of MCH Services and 2) reduction in maternal and child mortality. The programme consists in identifying high risk pregnant women, provide quality ante-natal care and referral support. The programme is implemented through the existing health infrastructure and functionaries, since January, 1988.

It would be too early toevaluate the impact on maternal and infant mortality, however, since the start of the programme, the coverage and utilization of services has markedly improved. Registration of pregnant women has increased upto 80.0 percent from mere 10.0 percent. 60-65.0 percent received prophylactic tetanus toxoid injections. The same proportion received blood examination, urine examination and blood pressure check-up which were earlier not done at the village level. Semi sterilised disposable delivery packs were used in more than 80.0 percent of deliveries.

The TBAs have played a major role.

The paper analyses the performance and the processes involved and future possibility of replication of the strategy in other parts.

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407 CANCER NEAR THREE MILE ISLAND

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Purpose: To investigate cancer risk (mainly leukemia, childhood malignancies) among 160,000 residents within a 10 mile radius of The Three Mile Island (TMI) nuclear power plant, in relation to releases from the 1979 accident and routine emissions.

Methods: Exposures were estimated from mathematical dispersion models that accounted for wind and terrain; accident emissions were validated against off-site dosimeters. Incident cancers in the period 1975-1985 (n=5493) were found by reviewing records of all local and regional hospitals. Preaccident and postaccident trends in cancer rates were examined in logistic analyses adjusted for age, sex, population density, income and education.

Results: For accident emissions, no associations were seen for leukemia in adults or for childhood cancers. For routine emissions, the odds ratios were raised for all childhood cancers and for childhood leukemia specifically but confidence intervals were wide (OR=1.5, 95% CI 0.7, 3.5; OR = 2.2, 95% CI 0.5, 8.6, respectively). The trend was negative for leukemia in adults. NonHodgkin's lymphoma and lung cancer showed raised risks in relation to both accident and routine emissions.

Conclusion: Overall, given the lack of clearcut effects on children and on radiosensitive sites like leukemia, the pattern of results does not provide convincing evidence that TMI releases influenced cancer risk during the limited period of follow-up.

408 CANINE LUNG CANCER AND PASSIVE EXPOSURE TO CIGARETTE SMOKE.

JS Reif, K Dunn, GK Ogilvie and CK Harris. Department of Environmental Health, Colorado State University, Fort Collins CO 80523 USA.

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A random sample of 300 males aged 30 to 70 years drawn from a household register of 2 villages were studied. A validated questionnaire was used to evaluate the presence or absence of these risk factors. The results were: $\bar{x}$ age 45 ± 10 (33-67 yrs)., $\bar{x}$ weight 50 ± 10 (37-93 kg) and $\bar{x}$ height 162 ± 5 (148-181 cm). Their mean systolic blood pressure (SBP) was 132 ± 22 (78-230 mmHg) and mean diastolic pressure (DBP) was 80 ± 12 (54-126 mmHg). Seventy two (24%) were told of having a raised blood pressure but only 34 (11%) were truly hypertensive (SBP > 160 and/or DBP > 95). Fifty seven (19%) had been on drug treatment at one time. One hundred seventy nine (60%) were smokers averaging 14 ± 8 sticks/day (1-40) and began smoking at a mean age of 18 ± 5 (10-40 yrs). The mean serum cholesterol was 4.5 ± 2 (2.2-8.9 mmol) in which 8 (2.6%) had hypercholesterolemia (> 7.0 mmol).

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In conclusion, in a rural Philippine community the most prevalent risk factor of cardiovascular disease is smoking. Hypertension is a moderately prevalent condition and high serum cholesterol level does not seem to be a significant risk factor. Therefore, the major thrust in the prevention of heart disease in this community should be the control of smoking.

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405 AN APPRAISAL OF INTEGRATED MOTHER AND CHILD HEALTH INTERVENTION PROGRAMME IN RURAL AREA OF RAJASTHAN

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A five year Integrated Mother and Child Health (MCH) Intervention Programme, with support of Indian Council of Medical Research (ICMR), is being implemented in rural block PHC area of Rajasthan State, covering 120,000 population. The Intervention Programme, based on risk approach, aims at 1) improving voverage, quality and utilization of MCH Services and 2) reduction in maternal and child mortality. The programme consists in identifying high risk pregnant women, provide quality ante-natal care and referral support. The programme is implemented through the existing health infrastructure and functionaries, since January, 1988.

It would be too early toevaluate the impact on maternal and infant mortality, however, since the start of the programme, the coverage and utilization of services has markedly improved. Registration of pregnant women has increased upto 80.0 percent from mere 10.0 percent. 60-65.0 percent received prophylactic tetanus toxoid injections. The same proportion received blood examination, urine examination and blood pressure check-up which were earlier not done at the village level. Semi sterilised disposable delivery packs were used in more than 80.0 percent of deliveries.

The TBAs have played a major role.

The paper analyses the performance and the processes involved and future possibility of replication of the strategy in other parts.

407 CANCER NEAR THREE MILE ISLAND

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Purpose: To investigate cancer risk (mainly leukemia, childhood malignancies) among 160,000 residents within a 10 mile radius of The Three Mile Island (TMI) nuclear power plant, in relation to releases from the 1979 accident and routine emissions.

Methods: Exposures were estimated from mathematical dispersion models that accounted for wind and terrain; accident emissions were validated against off-site dosimeters. Incident cancers in the period 1975-1985 (n=5493) were found by reviewing records of all local and regional hospitals. Preaccident and postaccident trends in cancer rates were examined in logistic analyses adjusted for age, sex, population density, income and education.

Results: For accident emissions, no associations were seen for leukemia in adults or for childhood cancers. For routine emissions, the odds ratios were raised for all childhood cancers and for childhood leukemia specifically but confidence intervals were wide (OR=1.5, 95% CI 0.7, 3.5; OR = 2.2, 95% CI 0.5, 8.6, respectively). The trend was negative for leukemia in adults. NonHodgkin's lymphoma and lung cancer showed raised risks in relation to both accident and routine emissions.

Conclusion: Overall, given the lack of clearcut effects on children and on radiosensitive sites like leukemia, the pattern of results does not provide convincing evidence that TMI releases influenced cancer risk during the limited period of follow-up.

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408 CANINE LUNG CANCER AND PASSIVE EXPOSURE TO CIGARETTE SMOKE.

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The risk factors associated with the development of primary canine lung cancer have been inadequately studied. A case-control study was conducted in order to determine whether passive exposure to environmental tobacco smoke was associated with an increased risk for the disease in dogs, as it is in humans. Cases (n=51) were obtained from two veterinary teaching hospitals and were confirmed histologically. Controls with other forms of cancer, not related to smoking in humans, were obtained from the same hospitals (n=83). Exposures assessed included the presence of a smoker in the home, the number of smokers, the amount smoked and the time spent by the subject indoors per day. The crude odds ratio for exposure to passive smoke was 1.49 (95% CI 0.7 -3.0), which fell to 1.32 (95% CI 0.6-2.8) after adjustment for state of residence. Additional adjustment for confounding by multiple logistic regression had little effect on the risk estimate. There was little evidence of a dose-response. An exposure index containing number of smokers, packs and time spent indoors was not related with increasing risk. Despite the weak nature of the relationship between passive smoke exposure and lung cancer risk in dogs, the study supports increased use of animal models as sentinels for human risk from environmental exposures.

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CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer. The papers at Tab 1 of this section of the notebook provide useful overviews of the variety of issues raised with regard to the spousal smoking studies.[1A-C]

For instance, in one of those major overviews, Smith, et al., (1992) write:[1C]

> Although epidemiology studies do not establish causal relationships, the spousal studies do not make clear whether the reported associations are indicators of risk of ETS exposure, indicators of risk of spousal smoking status, or methodological artifacts.

This section of the notebook addresses methodological issues raised in the literature by persons critical of the spousal smoking studies and the conclusions drawn from their data.

<u>Strength of the association</u>

- As Wynder and Kabat wrote in 1990:[1A]

> An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.

In epidemiology, weak associations call for special attention to possible sources of bias and confounding.

Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."[2]

- Exposure indices and risk estimates based on this type of information may be improper and incorrect.

- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.[2]

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Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.[3]

Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

- Smith, et al., comment on the importance of confounding factors:[1C]

> The reported relative risks or odds ratios have generally been no larger than 2.0, approximately the same magnitude as confounding lifestyle factors. In addition, there is evidence that many of these confounders are non-symmetrically distributed between smoking and nonsmoking households.

Use of questionnaires

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- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[4A,B] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.

- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[4C]

- As noted by Gori and Mantel (1991):[1B]

> Most epidemiologic studies have measured exposure by means of recall questionnaires, with results that are problematic even at qualitative levels. Aside from the inability of virtually all epidemiologic studies to define whether exposure or lack of it was correctly reported -- especially with data from proxy respondents -- the issues of intensity and duration of exposure have hardly been addressed by questionnaires. . . . [Q]uestionnaires have produced no more than rough indices of exposure.

<u>Histology</u>

- Lung cancer diagnoses were not always histologically or pathologically verified.[1A]

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- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).[1A]

- In a 1993 Letter to the Editor, Alan W. Katzenstein addresses the issue of disease misclassification, arising "when 'lung cancer cases' are not primary lung carcinomas but are secondary cancers that have metastasized to the lung." He calls diagnoses other than histology or cytology "equivocal, at best." Katzenstein illustrates the potential impact of disease misclassification using the Hirayama study, in which 89-100% of the cases "are of questionable disease classification": he proposes that if as few as four of the 163 "exposed" cases had been misclassified, the reported relative risk would be statistically nonsignificant.[5]

"Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.[1A] (This is sometimes called "data-dredging.")

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Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."

- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.[6]

Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a scientific symposium held in Argentina:

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological plausibility can be judged controversially.[7]

The eminent statistician Nathan Mantel concluded the following:

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[I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.[3]

In a 1991 review, Gio Gori and Nathan Mantel wrote:[1B]

It should be clear that the seemingly insurmountable difficulties in measuring ETS exposures and doses, unresolved classification bias, and the inability to control for numerous independent confounders explain the inconsistency of weak ETS epidemiologic results and speak against scientifically credible conclusions about a risk that, if real at all, remains imponderable.

Indeed, the only justifiable conclusion is that this issue cannot be resolved scientifically on the basis of currently available information.

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statements, are found at Tabs 1-7.

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CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.[8-21] They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.[8] When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.

- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.[9-12] When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.

- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.[8]

- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.[13-15]

- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable[8]; autopsy or histology results were available for only 11.5% (23 of 200) of the cases[8,16]; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable[8,12]; many possible confounding factors were overlooked.[8,17]

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.[18] In addition, Hirayama has not made his original data available for review.[8,19,20]

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-21. They are highlighted in yellow for useful information and in blue for adverse statements.

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CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.[22] Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).

- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.[8,24] According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."[23]

Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements, are found at Tabs 22-24.

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Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment*

E. L. Wynder and G. C. Kabat

Summary

The possibility that exposure to environmental tobacco smoke (ETS) may increase the lung cancer risk of nonsmokers has become a cause of public concern. It is unknown whether the levels of carcinogens in the diluted sidestream smoke of tobacco products that reach the nonsmoker's lung are sufficient to induce cancer. Available epidemiologic studies suggest a slight increase in the relative risk of lung cancer in nonsmokers due to exposure to ETS created by a smoking spouse. However, not all studies have found a significant association. The epidemiologic studies are examined in the light of the criteria of judgment of causality, including strength of association, consistency, temporality, methodological issues, and biological plausibility. Suggestions for further research, including studies in high-exposure populations and greater attention to histology, are proposed.

Introduction

Epidemiologists, chemists, biologists, physiologists, physicians, and public health officials have given much attention to the association of environmental tobacco smoke (ETS) exposure and the development of lung cancer in nonsmokers. A biological basis for such an association clearly exists because smoke constituents demonstrated to be carcinogenic in laboratory animals are inhaled and retained by the nonsmoker. Metabolites of tobacco-specific smoke constituents have been identified in the saliva, blood, and urine of nonsmokers after exposure to ETS (Greenberg et al. 1984; Hoffmann et al. 1984; National Academy of Sciences 1986; USDHHS 1987; Sepkovic et al. 1988). Several epidemiological studies have found a positive association between ETS exposure – usually defined as being due to a smoking spouse – and lung cancer (Hirayama 1981; Trichopoulos et al. 1981; Correa et al. 1983; Sandler et al. 1985; Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Pershagen et al. 1987). Other studies have found no significant association (Garfinkel 1981; Chan and Fung 1982; Koo et al. 1983; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986). No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

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H. Kasuga (Ed.) Indoor Air Quality

The epidemiological study of weak associations is burdened with problems that may yield artifactual positive findings or may show negative findings where a real association exists. The association of ETS and lung cancer risk, even if weak, would still be of concern as a public health problem in that most people are at one time or another exposed to smoke from burning tobacco products and the exhaled pollutants of tobacco smokers. A weak association in epidemiology requires careful examination and an understanding of the variables in question and all of the factors influencing the association (Wynder 1987).

In this overview we critically examine the published studies on ETS exposure and lung cancer to determine whether the evidence presented to date permits a sound conclusion as to causation.

General Exposure to ETS

At the outset we need to emphasize that an association between ETS and lung cancer must be deemed possible. A recent survey of self-reported exposure in a hospitalized population revealed that 66% of men and 60% of women had ETS exposure in childhood; 32% of the men and 61% of the women reported ETS exposure in the home in adulthood; and 60% of the men and 62% of the women who worked outside the home reported ETS exposure at work (Kabat and Wynder, unpublished data, 1987).

Critical Assessment

The first Surgeon-General's Report on Smoking and Health, published in 1964 (USPHS 1964), clearly delineated the criteria of judgment for causality. These criteria included: the magnitude of the association, consistency, temporality, and biological plausibility. Since these criteria were considered necessary to prove causation for a strong association, namely, active smoking and lung cancer, they should be equally required to determine the causality of weak associations (Wynder 1987). Let us examine the epidemiological evidence linking ETS with lung cancer in respect to these criteria.

Strength of the Association

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer (Table 1). If the observed relative risk is small, it is important to determine whether the effect could be due to biased selection of subjects, confounding, biased reporting, or anomalies of particular subgroups.

Consistency

If an association is real, internal consistency should be apparent within and between different studies. The majority, but not all of the studies of ETS and lung cancer have shown a positive association for ETS-exposure due to a smoking spouse (Table 1). In most of the studies, the confidence interval includes 1.0. While the prospective study by Hirayama (1981a) among Japanese women showed a significant association with the husband's smoking (largely adenocarcinomas), the prospective study among American

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Table 1. Summary of results of studies relating lung cancer risk in married women to their husbands' smoking habits

	Relative risk	95% Confidence interval
Prospective studies		
Hirayama (1981)	1.63	1.25–2.11
Garfinkel (1981)	1.18	0.90–1.54
Case-control studies		
Trichopoulos et al. (1981)	2.1	1.18–3.78
Chan & Fung (1982)	0.75	0.44–1.30
Correa et al. (1983)	2.03	0.83–5.03
Koo et al. (1983)	1.54	0.90–2.64
Kabat & Wynder (1984)	0.79	0.26–2.43
Wu et al. (1985)	1.2	0.6 –2.5
Garfinkel et al. (1985)	1.12	0.74–1.69
Lee et al. (1985)	1.03	0.41–2.47
Akiba et al. (1986)	1.48	0.88–2.50
Pershagen et al. (1987)	1.28	0.75–2.16

Table 2. Distribution of lung cancer by histologic groups in smokers and never-smokers. (From Kabat and Wynder 1984)

	Smokers		Never-smokers	
	Males (N = 1882) [%]	Females (N = 652) [%]	Males (N = 37) [%]	Females (N = 97) [%]
Kreyberg I	63	52	35	21
Kreyberg II	32	43	54	74
Mixed and undifferentiated/anaplastic	5	5	11	5

women by Garfinkel (1981) did not. It has been suggested that Japanese and American women are exposed to different levels of ETS due to different conditions in the two countries. Such differences could account for this disparity (Hirayama 1981b).

Within those studies presenting specific histologic analysis, differences exist in respect to the type of lung cancer involved. In active smokers, tobacco smoke exposure has a causative effect predominantly on squamous and small cell types of lung cancer (Kreyberg I), with a lesser, though still significant causative effect on the glandular type (Kreyberg II) (Wynder and Stellman 1977). Among nonsmokers, however, the glandular type of lung cancer predominates among both men and women (Kabat and Wynder 1984) (Table 2). The effect of ETS would thus be expected to be primarily responsible for the higher rate of adenocarcinomas among nonsmokers. The studies by Dalager et al. (1986) and Pershagen et al. (1987), however, suggest that the effect of ETS exposure is limited to induction of squamous cell lung cancer (Table 3). If this were, in fact, the case, then only the squamous or small cell type of lung cancer in nonsmokers

Table 3. Histology-specific odds ratios for spouse smoking from two studies

Study	Histologic type	N	Odds ratio	95% C.I.
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33– 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91– 9.10
	Other	18	1.31*	0.48– 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 –11.4
	Other	47	0.8	0.4 – 1.5

would be affected by ETS. Clearly, it is important that investigations of the effect of ETS exposure on lung cancer development in nonsmokers take histology into account, so as to determine whether an effect of ETS is limited to certain histological types.

Since smoking is more prevalent in lower income groups, at least among men, lung cancer in nonsmoking women in these groups should have a higher incidence. Thus, the influence of the level of education on smoking habits in the examined population needs to be considered as a possible confounder. Few studies to date have done this.

Methodological Issues

A particular concern in weak associations is reporting bias, that is, potentially differential reporting of exposures between cases and controls. In terms of ETS, does the lung cancer patient report exposure to tobacco smoke, be it at work, at home, at social functions, in childhood or adulthood, differently than the control? The case is likely to have a different attitude toward this question than does the control, a handicap not applicable to prospective studies. It needs to be determined whether the case's attitude towards questions on ETS exposure leads to under- or overreporting. Cases are likely to underreport their own smoking (Lee 1987), and they may tend to overreport their exposure to ETS and other potential hazards that could account for their illness. In studies that use proxy reports, different relatives may respond differently. Garfinkel et al. (1985) provides some insight into this phenomenon by showing that if the response came from the patient, the odds ratio was 1.0, if from the husband it was 0.92, and if from the daughter or son, 3.19 (Table 4). More work is needed on the validity of ETS-exposure information obtained from different relatives before we can evaluate which of these relative risks is closer to the truth.

In general, possible reporting bias represents a serious problem in case-control studies because it can produce a systematic artefact. It is particularly worrisome in that it cannot be effectively measured.

We also need to consider misclassification that can occur in both retrospective and prospective studies. Lee has proposed (Lee et al. 1986; Lee 1987) that the reported ETS effect on lung cancer risk can be explained by a misclassification of smokers as nonsmokers. According to these studies, a substantial percentage of respondents misrepresent their smoking habits. Using a 10.0% misclassification rate of ex-smokers as self-reported neversmokers coupled with the concordance of spouses' smoking habits,

Table 4. Data from Garfinkel et al. (1985) by type of respondent

	Husband's smoking habits at home		
	N of cases	OR	95% C.I.
Self	16	1.00	0.55- 1.74
Husband	34	0.92	0.63- 1.34
Daughter/son	48	3.19	0.91-11.19
Other	36	0.77	0.57- 1.03

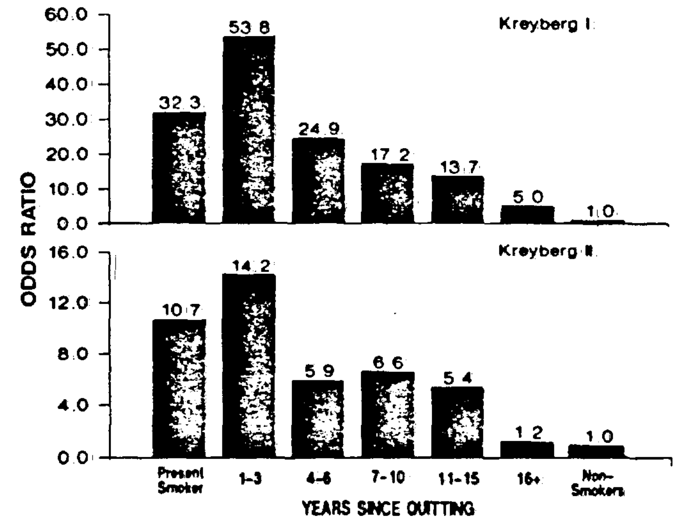

Fig. 1. Odds ratio of male ex-smokers for Kreyberg I (N = 687) and Kreyberg II (N = 301) lung cancer by years since quitting (controls = 6534). Source: American Health Foundation data

Lee calculated that an apparent increase in lung cancer risk can be obtained among nonsmokers married to smokers that approximates the increased risk observed in a number of epidemiologic studies (Lee 1987). At the extreme, Garfinkel et al. (1985) showed that 40% of lung cancer cases classified as "nonsmokers" in the hospital chart were in fact smokers as determined by interview. Although such a high rate of misclassification does not occur when cases are interviewed personally, to some extent denial is likely to occur even then, particularly among ex-smokers who had stopped smoking ten or more years ago. The risk of lung cancer among long-term ex-smokers, and even among ex-smokers who quit more than 16 years earlier, does remain elevated above the rate among those who never smoked (Fig. 1). Denial of past smoking may also not be uncommon in populations where smoking is or was socially unacceptable, as is the case among older Japanese women.

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Table 5. Percent of lung cancer cases who never smoked by histologic group (A.H.F. data)

	Males				Females			
	KI*		KII**		KI*		KII**	
	[%]	N	[%]	N	[%]	N	[%]	N
1969–1973	1.2	488	5.6	142	10.7	103	23.7	76
1974–1976	1.6	887	3.0	305	16.4	263	25.3	146
1977–1980	2.1	628	4.6	390	5.6	231	22.0	245
1981–1985	1.4	725	5.6	463	6.8	311	16.6	284

* Kreyberg I
** Kreyberg II

Another problem for epidemiologists involves subgroup analysis (Stallones 1987). Investigators are likely to examine numerous subgroups, and then prefer to present those subgroups that best fit the hypothesis. This tendency represents an inherent problem in epidemiology. The investigator should at a minimum give an idea of how many subgroups were originally examined and how many subgroups were discarded.

Temporality

One of the factors that led to the conclusion that active smoking causes lung cancer was that the increase in cigarette consumption preceded the increase in lung cancer rates, first in men and later in women. Enstrom (1979) has reported an increase in the lung cancer rate in nonsmokers over recent years, suggesting that factors in addition to personal cigarette smoking influence lung cancer mortality rates. The groups examined, however, are not strictly comparable, and misclassification of smokers as nonsmokers in the national surveys needs to be considered. Our data from a long-term, hospital-based case-control study do not indicate an increase in the percentage of male nonsmokers with lung cancer in either of the two main histologic groupings (Kreyberg I and II) over the last 30 years (Table 5).

In fact, the percentage of nonsmokers with lung cancer among women has declined, which may be a consequence of the diminishing pool of women who have never smoked.

Biological Plausibility

Several studies have demonstrated that most tumorigenic agents are present in undiluted sidestream smoke in higher concentrations than in mainstream smoke (Hoffmann et al. 1983; National Academy of Sciences 1986; Hoffmann and Wynder 1986) (Table 6). Biochemical studies indicate that nonsmokers exposed to ETS have levels of nicotine or cotinine in the blood or urine that are about 1/100th the level seen in active smokers (Table 7) (Jarvis et al. 1984; National Academy of Sciences 1986). Some of the nicotine measured in the blood and urine represents nicotine that is absorbed by the saliva of nonsmokers and does not reach the lung directly (Jarczyk et al. 1987). It is important to

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Table 6. Distribution of compounds in undiluted cigarette mainstream smoke (MS) and sidestream smoke (SS)

Nonfilter cigarettes

	MS	SS/MS
(A) Vapor phase		
Carbon monoxide	10 – 23 mg	2.5– 4.7
Carbon dioxide	20 – 40 mg	8 – 11
Benzene	20 – 50 μg	10
Formaldehyde	5 – 100 μg	0.1–≃50
Acrolein	50 – 100 μg	8 – 15
Acetone	100 – 250 μg	2 – 5
Hydrogen cyanide	400 – 500 μg	0.1– 0.25
Hydrazine	24 – 43 ng	3.0
Ammonia	50 – 170 μg	40 – 170
Methylamine	11.5 – 28.7 μg	4.2– 6.4
Nitrogen oxides	50 – 600 μg	4 – 10
N-nitrosodimethylamine	10 – 180 ng	20 – 100
N-nitrosopyrrolidine	2 – 110 ng	6 – 30
(B) Particulate phase		
Particulate matter	15 – 40 mg	1.3– 1.9
Nicotine	1 – 2.5 mg	2.6– 3.3
Phenol	60 – 140 μg	1.6– 3.0
Catechol	100 – 350 μg	0.6– 0.9
Hydroquinone	110 – 300 μg	0.7– 0.9
Aniline	360 ng	30
2-Toluidine	30 – 160 ng	19
2-Naphthylamine	4.3 – 27 ng	30
4-Aminobiphenyl	2.4 – 4.6 ng	31
Benz(a)anthracene	40 – 70 ng	2 – 4
Benzo(a)pyrene	10 – 40 ng	2.5– 3.5
N'-Nitrosonornicotine	120 –3,700 ng	0.5– 3
NNK	120 – 950 ng	1 – 4
Cadmium	100 ng	7.2
Nickel	20 –3,000 ng	13 – 30
Polonium-210	0.03– 1.0 pCi	?

note that nicotine occurs in ETS primarily as a vapor phase constituent rather than in the particulate matter of the aerosol as is the case in mainstream cigarette smoke (Eudy et al. 1987). Measurement of nicotine or its metabolites will, therefore, not reflect the proportional uptake of particulate matter from ETS. In the light of our present knowledge of dose-response in carcinogenesis and because the carcinogenic activity of tobacco smoke as measured in animal systems is relatively low, the question needs to be raised whether the carcinogenic potential of inhaled ETS suffices to induce lung cancer. Hoffmann and Hecht (1985) have proposed nicotine-derived nitrosamines in ETS as organ-specific carcinogens for the lung. It is possible that these chemicals reach the lungs in sufficient dose to induce neoplastic changes. These carcinogens may also be formed endogenously from inhaled or ingested nicotine and appropriate nitrosating agents (Hoffmann and Hecht 1985). Tumor promoters are less likely to play a role in ETS

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Table 7. Approximate relations of nicotine as a parameter between non-smokers, passive smokers and active smokers[a]. (From Jarvis et al. 1984)

Nicotine/cotinine	Non-smokers without ETS exposure No. = 46		Non-smokers with ETS exposure No. = 54		Active smokers No. = 94
	Mean value	% of active smokers value	Mean value	% of active smokers value	Mean value
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml)					275
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[a] Differences between non-smokers exposed to ETS compared with non-smokers without exposure
* $p < 0.01$
** $p < 0.001$

carcinogenesis than in active smoking because of their much lower concentration. In general, tumor promoters are effective only when applied repeatedly in relatively large amounts.

In considering the existing data on ETS exposure and lung cancer, it is noteworthy that Auerbach et al. (1961) showed only minor histological changes in the bronchial epithelium of nonsmokers and found that the ciliated columnar epithelium that covers their bronchi were largely intact. Deposition of carcinogenic smoke particulates can take place only upon inhibition of the protective functioning of the lung clearance system. Squamous cell lung cancer can arise only from ciliated columnar cells that have undergone squamous metaplasia.

An active smoker with each puff from a cigarette inhales a volume of 35–50 ml of a concentrated aerosol containing 3–5 billion particles per ml that adversely affect the protective cilia and mucous defense system of the bronchi (Ferin et al. 1965). The passive smoker is at no time exposed with such force to such a highly polluted inhalant. Furthermore, ETS particles are more likely to be deposited in the upper respiratory tract and not predominantly in the bronchi as is the case in active smoking. Thus, our respiratory defense system may be able to deal more readily with the relatively lighter deposition of particles and exposure to volatiles in ETS, as the observation by Auerbach et al. (1961) would suggest.

Future Studies

Future epidemiological studies on the association of ETS with lung cancer should attempt to avoid the pitfalls discussed above. The definitive evidence that a factor causes

human cancer requires support from descriptive, metabolic, and molecular epidemiology.

Beyond extension of prospective studies, such as those now in progress by Garfinkel and Stellman at the American Cancer Society, we suggest:

1) Continuing ongoing case-control studies with special reference to histologic type and careful consideration of methodological issues.
2) Estimating the relative importance of ETS exposure in different settings – in the home, in the workplace, in social situations, and during transportation.
3) Further studying lung cancer rates among pipe and cigar smokers, and, if feasible, among nonsmokers exposed to ETS from these products.
4) Studying lung cancer incidence in groups occupationally exposed to high levels of ETS at their worksite such as waiters, bartenders, train conductors, airplane personnel, and office workers.
5) Studying bronchial epithelium in autopsy material of established never-smokers whose exposure to ETS is known.
6) Determining the incidence of lung cancer by histological type in confirmed never-smokers.
7) Comparing the presence of adducts of tobacco-specific carcinogens with DNA in smokers, passive smokers, and "never-smokers" (Hoffmann and Hecht 1985; Hecht et al. 1987).

In summary, verification of the possible association of ETS and lung cancer represents an important challenge to epidemiologists, laboratory scientists, and public health authorities. The public is entitled to inhale the cleanest possible air regardless of whether ETS is proven to be cancer-inducing. Additional efforts on the part of epidemiologists are required to firmly establish the nature and significance of the reported associations between passive smoking and lung cancer.

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Mainstream and Environmental Tobacco Smoke

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Environmental tobacco smoke (ETS) is derived from cigarette smoldering and active smoker exhalation. Its composition displays broad quantitative differences and redistributions between gas and respirable suspended particulate (RSP) phases when compared with the mainstream smoke (MSS) that smokers puff. This is because of different generation conditions and because ETS is diluted and ages vastly more than MSS. Such differences prevent a direct comparison of MSS and ETS and their biologic activities. However, even assuming similarities on an equal mass basis, ETS-RSP inhaled doses are estimated to be between 10,000- and 100,000-fold less than estimated average MSS-RSP doses for active smokers. Differences in effective gas phase doses are expected to be of similar magnitude. Thus the average person exposed to ETS would retain an annual dose analogous to the active MSS smoking of considerably less than one cigarette dispersed over a 1-year period. By contrast, consistent epidemiologic data indicate that active smoking of some 4–5 cigarettes *per day* may not be associated with a significantly increased risk of lung cancer. Similar indications also obtain for cardiovascular and respiratory diseases. Since average doses of ETS to nonsmoking subjects in epidemiologic studies are several thousand times less than this reported intake level, the marginal relative risks of lung cancer and other diseases attributed to ETS in some epidemiologic studies are likely to be statistical artifacts, derived from unaccounted confounders and unavoidable bias.

INTRODUCTION

During the last decade, considerable attention has been devoted to the question of whether environmental tobacco smoke (ETS) causes disease in nonsmokers (USSG, 1986; NRC, 1986; EPA, 1990a). Some epidemiologic studies of nonsmokers presumably exposed to ETS have suggested a marginal increase of risk for some diseases previously associated with active mainstream smoking (MSS). These reported risks, however, border on statistical and epidemiologic insignificance, and could easily derive from numerous and documented biases and confounders.

Official reviews have stopped short of implying a causal role of ETS in most of these associations, with a notable exception for lung cancer. This exception has been based not so much on admittedly questionable epidemiology, but on a public health stance of concern driven by perceived—but largely undocumented—compositional similar-

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ities of ETS and MSS, and by the implausible assumption that no dose exists below which risks are nonexistent or imponderable (USSG, 1986; NRC, 1986; IARC, 1987; EPA, 1990a,b).

This study analyzes the scientific literature on the chemical and physical characteristics of MSS and ETS, their reported specific biologic activities, and the mean relative doses of active MSS smokers and ETS-exposed nonsmokers under prevailing real life conditions, and finally considers the epidemiologic projections that these combined influences imply.

PHYSICAL AND CHEMICAL CHARACTERISTICS OF MSS AND ETS

Mainstream smoke is what smokers generate and inhale. Cigarettes smoldering between puffs emit side stream smoke (SSS), which, along with smoke exhaled by active smokers (EMS), becomes environmental tobacco smoke after immediate and progressive dilution, and aging. Both MSS and ETS result from the combustion of the same substrate and lead to exposures to analogous but not necessarily the same components, and certainly in different proportions, under different physical conditions, and at very different doses.

MSS is generated and exists in the well-defined confines of the cigarette and the mouth and the respiratory system of smokers. It is formed under conditions of high relative humidity, results in particulates with mean aerodynamic diameter of about 0.7 μm (Hiller *et al.*, 1982), and is inhaled within a few seconds of its formation with little aging or intervening transformations. All this permits a rather precise definition of its chemical and physical nature (Dube and Green, 1982).

On the other hand, any characterization of ETS must recognize its unstable and variable nature. The immediate dilution of side stream smoke with air begins a chain of physical and chemical transformations that continuously alter the ensuing ETS as it ages over hours. Smoker-exhaled mainstream smoke also contributes to ETS a certain fraction of gases and the small respirable suspended particulates (RSP) that are not retained in the lungs of smokers (Baker and Proctor, 1990). Actual SSS itself is difficult to define because its composition has been shown to vary under different conditions of experimental generation (Brunnemann *et al.*, 1978; Eatough *et al.*, 1990). Moreover, SSS is not indicative of the physical and chemical changes that occur in ETS as it continuously dilutes and ages.

The experimental generation of SSS-ETS in laboratory chambers after the smoldering of a few cigarettes has provided some clues to the composition of ETS (Benner *et al.*, 1989; Eatough *et al.*, 1989; Ingebrethsen *et al.*, 1988; Pritchard *et al.*, 1988; Vu-Duc and Huynh, 1989; Ingebrethsen and Sears, 1985). Better experiments have been attempted in larger chambers where humidity, temperature, ventilation rates, and other variables could be controlled, also leading to a perception of the differential influence of these variables on ETS decay (Eatough *et al.*, 1990; Baker and Proctor, 1990; Tang *et al.*, 1988; Ingebrethsen *et al.*, 1988). However, such data still fail to represent actual life conditions in real environments with a multismoker presence. No comprehensive studies have been published so far under such natural settings. The few available reports have attempted to measure only selected chemicals, sampled over variable but generally short periods of time, making them of dubious relevance to situations of prolonged exposure (Proctor *et al.*, 1989a,b; Lofroth *et al.*, 1988; Carson and Erikson, 1988; Sterling *et al.*, 1988; Oldaker *et al.*, 1987; Stehlik *et al.*, 1982). In the future,

more useful data should come from real-life ambient conditions with smokers being present, where new ETS is continuously generated as aging ETS decays, eventually establishing quasi-steady-state conditions and an "average" chemical and physical composition of ETS. Thus far, only nicotine and RSP concentrations have been measured with some appearance of accuracy under such conditions.

While several thousand MSS components have been identified in the literature, only about 100 components of fresh SSS and EMS have been measured. In addition, only fragmentary information is available for diluted ETS components, most of which appear to be present—if at all—at levels beyond analytical capabilities (Guerin *et al.*, 1987; NRC, 1986; USSG, 1986; EPA, 1990a). Today only a few specific and some general inferences are possible about the differences of MSS and ETS. SSS, from which ETS mainly is derived, is generated under conditions of better oxygenation and contains proportionally less carbon monoxide than MSS. It also contains fewer products of pyrolysis and distillation, and undergoes immediate cooling and vast dilution with air, with the result that ETS-RSP have considerably smaller size than MSS-RSP, with mean aerodynamic diameters on the order of 0.1 μm, or 100 to 200 times smaller in volume than MSS-RSP (Ingebrethsen *et al.*, 1988; Ingebrethsen and Sears, 1985). Smaller particles tend to evaporate faster and more efficiently than larger ones, so that many substances associated with MSS-RSP are more prevalent in the gas phase of ETS. This and the somewhat more alkaline conditions of SSS cause nicotine to appear in the ETS gas phase almost exclusively, while it is mainly associated with particulates in MSS.

As ETS ages, particle concentration and total mass decrease because smaller particles eventually coalesce, while mass is lost to diffusion/evaporation and to electrostatic and gravitational deposition (Hinds, 1978; Benner, 1989). The process continues with dynamics that depend on temperature, pressure and relative humidity, electrostatic conditions, ambient geometry and surface composition (furniture, fabrics, paints, crowding, etc.), ventilation rates, type and number of cigarettes smoked, mode of smoking, and other variables (Baker and Proctor, 1990).

In time, ETS gases and RSP adsorb to ambient surfaces and are disposed of by ventilation, while adsorbed substances may again desorb and recirculate in gas or vapor form, as has been suggested to happen with nicotine. Complex chemical transformations also occur because of interactions among molecules, oxidation, and probably photochemistry when UV radiation is present (Proctor, 1990). These continuous transformations occur at rates peculiar to each environmental situation and therefore result in physical states and chemical compositions that can be substantially different from place to place and from time to time.

In general, the better measures and estimates of ETS pertain to suspended particulates, a complex of substances that is apparently more stable and more measurable than individual substances. MSS-RSP appears to contain the smoke fractions capable of producing certain tumors in experimental animals. However, given that ETS and MSS have substantial differences in component concentration and partitions between gas and particulate phases, the issue of their relative biologic activity cannot be answered beyond some sensible conjecture. Past and also recent laboratory studies indicate that the biologic potencies of MSS-RSP and SSS-RSP seem virtually equivalent, with no detectable potency noted in the semivolatile fractions (Grimmer *et al.*, 1988; Stanton *et al.*, 1972). These data, however, pertain to the relative position of MSS-RSP and SSS-RSP condensates, and their relationship to ETS-RSP condensates has not been resolved. Other studies have reported that the *in vitro* mutagenic activity of MSS and

ETS may be roughly comparable, although the biologic significance of such data is speculative (Claxton *et al.*, 1989).

MEASUREMENT OF EXPOSURE

In the case of MSS the relative ratios of smoke components remain comparatively stable. Based on internal markers, the measurement of exposure and dose intake has been reasonably well defined, especially as pertains to RSP, nicotine, carbon monoxide, and other specific components (Gori, 1990). However, and despite several attempts at definition, selected markers have been rather disappointing surrogates for total ETS intake or exposure estimates.

A reasonable environmental marker should be specific to ETS, be easily detectable, and have a nearly constant ratio to other ETS components (NRC, 1986). Given the variable chemical and physical nature and the extreme dilution of most components of ETS, it is not surprising that a satisfactory marker of exposure has not been identified. For that and other reasons, an internal marker of actual ETS intake or dose has proven to be even more difficult to identify.

Most epidemiologic studies have measured exposure by means of recall questionnaires, with results that are problematic even at qualitative levels. Aside from the inability of virtually all epidemiologic studies to define whether exposure or lack of it was correctly reported—especially with data from proxy respondents—the issues of intensity and duration of exposure have hardly been addressed by questionnaires. Even when problems of subject misclassification, respondent bias, and correction for background ETS exposure could be addressed, questionnaires have produced no more than rough indexes of exposure. The collection of dependable information on actual doses at specific target sites and at different times has not been possible (Wu-Williams and Samet, 1990; Cummings *et al.*, 1989; McCarthy *et al.*, 1987).

Hopes have been placed on nicotine and its metabolite cotinine as possible markers of ETS intake and actual internal dose (Cummings *et al.*, 1990; Jarvis, 1989; Coultas *et al.*, 1987; Jarvis *et al.*, 1985; Hoffmann *et al.*, 1984). Unfortunately ETS-nicotine resides mostly in the gas phase and decays at rates quite different from other ETS components, to which it will have ratios that are variable in time and largely unpredictable (Tang *et al.*, 1988). Plasma cotinine levels suffer from similar and other shortcomings, although they have been shown to correlate with self-reported exposure to ETS (Cummings *et al.*, 1990; Jarvis, 1989). Reports also suggest that physiologic clearance of nicotine and cotinine at low plasma levels may proceed at much slower rates, likely because of slower release from preferential body compartments (Lewis *et al.*, 1990). Until these low-level kinetics are better understood, low plasma levels of nicotine and cotinine are likely to lead to substantial overestimations of intake doses. As such, nicotine and cotinine may provide a dichotomous index of contemporary exposure, but they remain inadequate as quantitative estimators of exposure, actual ETS dose, or their variation over an individual's life.

The ratio of ETS-nicotine to ETS-RSP has been suggested as a possible means to determine RSP intake from plasma nicotine levels, but such ratios appear too variable to be useful (Oldaker *et al.*, 1989). DNA and protein adducts have been proposed as markers of internal ETS dose, even though their specificity to ETS and their relationship to disease, especially to cancer, are in question (Randerath *et al.*, 1989; Harris *et al.*, 1987). Moreover, recent studies have reported no increase in DNA adducts in non-

smokers exposed to ETS (Holz *et al.*, 1990). The reported mutagenicity of urine samples in ETS-exposed nonsmokers also has proven elusive as a marker, largely because results may not be distinguishable from background rates and because of interferences from dietary sources (Scherer *et al.*, 1987, 1989; Mohtashamipur *et al.*, 1987; Sorsa *et al.*, 1985).

There has been great interest in measuring ETS-RSP directly, since its physical properties make for more positive identification and because biologic activity may reside specifically in the particulate phase, both in terms of its components and in terms of its longer residence time and cellular contact in the lungs. However, suspended particulates in air may be derived from many sources, and measurements of ETS-RSP need to be corrected for non-ETS RSP background. Several studies have reported differential values in the same settings under smoking and nonsmoking conditions (Repace and Lowrey, 1980; Weber and Fisher, 1980; Sterling *et al.*, 1987; Miesner, 1988; Kirk *et al.*, 1988a,b; Turner, 1988). It is obviously difficult to duplicate conditions of room occupancy, clothing, human traffic, ventilation, etc., where the only changing variable is smoking or not smoking. These problems have been much discussed, so that greater credibility can be accorded to the latest published studies. According to the more recent measurements of ETS-RSP in homes and workplaces, and allowing for differences of nonsmoking and smoking situations, a liberal estimate of ETS-attributable-RSP mean concentration in ambient air is less than 50 $\mu g/m^3$ (Table 1).

In regard to exposure to ETS gas phase components, it is enlightening to compare the concentrations of representative ETS components with the corresponding threshold limit values (TLVs), as established by the American Conference of Governmental and Industrial Hygienists for workplace safety. Incidentally, such values include considerable safety factors and are usually lower than the permissible exposure levels (PELs) established by the National Institute for Occupational Safety and Health (NIOSH)

TABLE 1

CONCENTRATIONS OF RSP FROM ETS AND OTHER SOURCES IN VARIOUS ENVIRONMENTAL SETTINGS WITH AND WITHOUT SMOKER PRESENCE

		RSP concentration ($\mu g/m^3$)	
Reference	Site	No smoking	Smoking
Coultas *et al.* (1990a)	Homes	NA	17
Sheldon *et al.* (1989)	Homes	22[a]	65[a]
Spengler *et al.* (1981)	Homes	NA	20
Spengler *et al.* (1985)	Offices	39[b]	72[a]
Proctor *et al.* (1989b)	Offices	8[b]	23[b]
Oldaker *et al.* (1990)	Offices	NA	27[b]
Miesner (1988)	Offices	15[a]	36[a]
Sterling *et al.* (1983)	Office buildings	15[a]	29[a]
Coultas *et al.* (1990b)	Workplaces	NA	64[a]
Oldaker *et al.* (1990)	Restaurants	NA	36[b]
Crouse (1988)	Restaurants	NA	34[b]
Proctor (1990)	Public transport	14[b]	36[b]

Note. NA, data not available or not applicable.
[a] Based on total RSP.
[b] Based on UV-RSP portion of total RSP.

and the Occupational Safety and Health Administration (OSHA). Table 2 gives some examples for selected indicator substances representative of related chemical families.

The estimates in Table 2 assume maximum recorded SSS emissions, no ventilation, no surface adsorption, and no intervening decay of any sort. However, official reports give estimates of the range of the ratios of MSS/ETS concentrations for selected components (NRC, 1986). These were found to vary as follows:

	MSS/ETS ratios		
Nicotine	57,333	to	7,200,000
Benzo[*a*]pyrene	68	to	40,740
Acrolein	1,500	to	20,833
Benzene	112	to	7,167
Acetone	240	to	2,000

Such values show the extremes of dilution that ETS has displayed under various conditions, and suggest that the number of cigarettes required to attain TLVs under realistic conditions would be orders of magnitude higher than the conservative estimates listed in Table 2.

ESTIMATING RELATIVE DOSES OF MSS AND ETS RSP

Although certain assumptions are necessary in estimating ETS-RSP doses, they are based on simple facts or on measurements that are fairly well verified. With this in

TABLE 2

ESTIMATED NUMBER OF CIGARETTES REQUIRED TO REACH TLV LEVELS FROM SSS EMISSION OF SELECTED CHEMICALS IN A SEALED AND UNVENTILATED 100-m^3 ENCLOSURE

SSS component	SSS output[a] (mg/cigarette)	TLV[b] (mg/m^3)	Cigarettes required
Methylchloride	0.88	10.30	1,170
Hydroquinone	0.16	2	1,250
Cadmium	0.0007	0.01	1,430
Acetaldehyde	1.26	180	1,430
Acetic acid	1.5	25	1,660
Nitrogen oxides	2.8	50	1,780
Formic acid	0.525	9.4	1,790
Pyridine	0.39	16	4,100
Phenol	0.25	19	7,600
Methylamine	0.1	13	13,000
Benzene	0.24	32	13,300
Catechol	0.14	23	16,500
Nickel	0.0025	1	40,000
Dimethylamine	0.036	18	50,000
Hydrazine	0.00009	0.13	145,000
Acetone	1	1780	178,000
Benzo[*a*]pyrene	0.00009	0.2[c]	222,000
2-Toluidine	0.003	9	300,000
Polonium 210	0.4 pCi	3 pCi/liter[d]	750,000
Toluene	0.000035	375	1,000,000

[a] Data from EPA (1990a), Table C-2, pp. C-19 and 20.
[b] Data from ACGIH (1990).
[c] Based on the TLV for coal tar pitch volatiles.
[d] EPA (1990c).

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mind, such estimates seem reasonably realistic and less affected by obvious judgmental considerations. Nevertheless, in comparing RSP doses from ETS and MSS exposures it also seems reasonable to present results in analog form rather than as precise point estimates, in recognition of possible uncertainties.

Assuming a prolonged daily exposure of 10 hr, a typical person would be exposed to a daily ETS-RSP dose of roughly 0.3–0.4 mg after breathing ambient air with a 50 $\mu g/m^3$ ETS-RSP concentration, at the rate of about 0.7 m^3/hr (Crawford-Brown, 1987). This is equivalent to over a 1000-fold reduction compared with the inhaled dose of the average mainstream smoker.[2]

However, an important difference relates to aerodynamic particle size, which tends to reduce lung retention of the smaller and probably less charged ETS-RSP particles (USSG, 1986). Indeed, available studies indicate an 80–90% efficiency of retention of mainstream smoke RSP in the lungs of smokers (Mitchell, 1962; Dalhamn *et al.*, 1969; Hinds *et al.*, 1983), while other studies show that only some 10% of RSP may be retained in the lungs of ETS-exposed subjects (Hiller *et al.*, 1982). This retention differential has been recognized by the EPA (EPA, 1990a), even though reliable studies suggest a substantially greater difference (McAughey *et al.*, 1989, 1990; Crawford and Eckerman, 1983). Therefore, based on mass alone, the average dose of ETS-RSP retained in the lung may be less than 1/10,000 of average MSS-RSP smoker doses.

RSP retention, however, does not equate with tissue or individual cell dose, which is the important issue given that cancer is thought to begin with cellular events. Among other things, cell dose will depend on quantity available per cell, proximity to cell surface, cell surface exposed, cell surface permeability, and duration of contact. Cellular dose is therefore modulated by mucociliary clearance and by the permeability of lung epithelium (Gerde *et al.*, 1991). In this regard, published data indicate that average mucociliary clearance is some threefold greater in nonsmokers than in smokers (Vastag *et al.*, 1985; Foster *et al.*, 1985), while average airway mucosal permeability appears to be about one third as great in nonsmokers as in smokers (Kennedy *et al.*, 1984), probably as the result of a thicker and more viscous mucous layer (Zayas *et al.*, 1990). Although these studies involve a relatively small number of subjects, they indicate that the effective cellular dose in ETS-exposed nonsmokers may be further reduced by close to 90% when compared with active smokers, due to clearance and permeability factors alone.

Together, these considerations suggest that the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over a 1-year period (see Footnote 2).

MSS AND ETS: EPIDEMIOLOGIC COMPARISONS

An annual ETS retained dose equivalent to the active smoking of less than one cigarette over the course of 1 year may be compared with the MSS dose/response associations reported with various health conditions. The limit of statistical significance

[2] The average smoker of 30 cigarettes per day inhales some 30 mg of nicotine (Gori and Lynch, 1985). The sales-weighted average tar/nicotine ratio for the smoke of commercial cigarettes is 15–18 (FTC, 1985). Therefore the average smoker inhales about 500 mg of tar daily.

TABLE 3

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH LUNG CANCER RISK IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)

Reference	Maximum cigarettes/day
British doctors[a]	6.3
Swedish men[b]	3.9
ACS, 9 states[c]	5.4
ACS, 25 states[b]	0.9
U.S. veterans[c]	0.6
Canadian veterans[c]	1.6
Japanese men[b]	3.1
California men[c]	7.0

[a] From Doll and Peto (1978).
[b] From USSG (1979), pp. 5–13, Table 2.
[c] From USSG (1982), p. 38, Table 6.

for such associations would provide a reasonable index of comparison. For lung cancer, data from independent studies listed in U.S. Surgeon General Reports yield the results in Table 3, after analysis by standard analytical procedures.[3]

Official sources refer to the British doctors study as the most reliable set of data for dose/response analysis (EPA, 1990a). This prospective study appears to be adequately documented and offers a reasonably accurate tracing of subjects (Doll and Peto, 1978). Thus, data in Table 3 indicate that the active smoking of 4–5 cigarettes/day is not likely to be statistically associated with elevated lung cancer risk. This assessment, presented here without undue claim of precision, is in accord with other estimates (Wynder, 1991). It suggests that since ETS retained doses are several thousand times less than MSS doses from this level of cigarette smoking, they appear insufficient to generate elevated risks of lung cancer.

This conclusion is consistent with an increasing body of scientific opinion that MSS may act as a weak promoter rather than as an initiator, supporting the implication of no observable epidemiologic risk at low doses (Albert, 1989; Doll and Peto, 1981;

[3] Individual studies were analyzed separately. Generally, for each study, the relative risk associated with the number of cigarettes consumed daily was listed. The first step in the analysis was to fit the data to a function of the form

$$RR = A_0 + A_1X + A_2X^2,$$

where RR is the relative risk, A_0, A_1, and A_2 are coefficients calculated by the maximum likelihood method, and X is the daily cigarette consumption. Cigarette consumption data are usually expressed in intervals, e.g., 1–9. The midpoint or the mean value of each interval × 1.25 was used in the calculation, justified by studies which indicate an average 30% underreporting of daily cigarette smoking (Hatziandreu *et al.*, 1989; La Vecchia, 1986; Jackson and Beaglehole, 1985). The highest consumption values are generally reported as open-ended, e.g., 40+, and here the midpoint was set at the given value plus 10. For the British doctors study the actual mean values of the intervals were available (Doll and Peto, 1978). The nonsmoker reference data points (0,1) were also entered in the regressions. Although other functions were examined, graphic and statistical analysis shows that the quadratic function provides an exceptionally good fit to the data, with a corrected multiple coefficient of determination close to 1 in each case. Critical values of daily cigarette consumption were calculated as the values at which the lower bound of the 95% confidence interval of the estimated RR was unity.

TABLE 4

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH RISK FOR CORONARY HEART DISEASE MORTALITY IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)*

Reference	Maximum cigarettes/day
U.S. veterans	1.5
ACS, 9 states	2.5
Japanese men	4.0
Canadian veterans	4.5
British physicians	4,5
Swedish men	2.5
California men	3.0
Swiss physicians	3.0

* Epidemiologic data from USSG (1983), p. 118.

Doll, 1978). Moreover, epidemiologic studies of MSS categorize exposure by number of cigarettes smoked, report multiannual exposure durations, and provide some evidence of commensurate latency times preceding diagnosis. By contrast, most nonsmokers in households may be exposed to ETS for only a few hours a day, which would further tend to increase the distance between MSS and ETS doses.

The daily levels of cigarette consumption compatible with no significantly increased risk for other diseases associated with active smoking appear to be of the same order as for lung cancer. Tables 4 and 5 report the analogous estimates for cardiovascular and respiratory disease mortality, with the implication that retained doses of ETS are unlikely to be associated with significant risk elevations for such diseases as well.

CLOSING REMARKS

Ordinarily it is extremely difficult to demonstrate the effects of an agent at low dose levels. Rather, after an effect becomes apparent at high doses, the interpretation is

TABLE 5

MAXIMUM LEVELS OF DAILY CIGARETTE CONSUMPTION AT WHICH RISK FOR RESPIRATORY DISEASE MORTALITY IN MALE SMOKERS MAY NOT BE SIGNIFICANTLY INCREASED FROM THE RISK OF NONSMOKERS, BASED ON EPIDEMIOLOGIC DATA (SEE FOOTNOTE 3)*

Reference	Maximum cigarettes/day
Chronic bronchitis	
U.S. veterans	5.5
Canadian veterans	2.6
Emphysema	
U.S. veterans	2.2
Canadian veterans	2.7
California men	5.5
Bronchitis and emphysema	
British physicians	3.0
U.S. veterans	

* Epidemiologic data from USSG (1984), p. 202.

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made that some effect, however small, would obtain at lower levels. Using some dose/response model an estimate of the effects at low doses, often including some statistical confidence intervals, is attempted.

The difficulty with low level determinations is that often the results fail to be significantly different from the null reference. In other words, the confidence limits of the effect would likely include the null reference, and/or the actual estimate of the effect might even be in the direction of protection instead of harm. Indeed, for most substances there is some threshold of tolerance below which the organism can cope without suffering adverse effects. For that matter it is apparent that levels at or below threshold might actually be beneficial in the sense of inducing and stimulating resistance, a process known as hormesis. This is in fact the case for virtually all beneficial and even essential substances, which would produce adverse effects when administered at excessive doses.

The ETS of public health concern is what is presented to average nonsmokers under commonplace environmental conditions and not the exceptional examples that can be created in laboratories. With this stipulation, ETS is a very elusive entity, undergoing continuous transformations at extremes of dilution that make efforts to define its chemical, physical, and biologic characteristics highly difficult. While the components of MSS/SSS may also be present in ETS, it is also clear that with few exceptions they are undetectable by the most sophisticated analytical procedures.

Despite these rarefied dilutions, an ETS hazard has been presumed from a conjectural association with MSS (EPA, 1990a,b; USSG, 1986; NRC, 1986). Central to this conjecture is the presumption of an equivalent chemical and biologic activity of MSS and ETS, and of the absence of low doses below which risk would be null or intangible. However, current understanding of composition alone is not sufficient to compare activities among MSS, SSS, and ETS, and the actual testing in biological systems suffers for two main reasons: the need to utilize concentrated laboratory surrogates that may have little relevance to actual ETS, and the unresolved obstacles to interpreting high-dose-related animal or *in vitro* data in terms of equivalent human responses at extremely low doses.

With this in mind, and even assuming that the biologic activities of MSS and ETS are of similar order, the reality of the extreme dilution of ETS remains. In this regard we have noted that current regulations allow workplace exposures to many ETS gas phase constituents at concentrations between thousands of and a million times higher than can be expected from commonplace ETS.

We also offered evidence that if epidemiologic investigations of MSS and lung cancer had been confined to the effects of exposure to a few cigarettes daily, they would have failed to yield significant risk signals. Similar evidence has been shown to hold for other diseases associated with active MSS smoking. At the same time it is apparent that subjects included in ETS epidemiologic studies were probably exposed to equivalent MSS-RSP doses below even a single cigarette *per year*. Therefore, marginal RR values associated with ETS exposures should be imputed to biases, confounders, and other weaknesses of the investigations, and any judgment that ETS exposure leads to lung cancer and other diseases would flow from argument, not from credible data.

In fact, the majority of epidemiologic studies of ETS suffer from what appear to be irreparable deficiencies. Earlier on we discussed the failure of epidemiologic studies in general to define exposure to ETS in terms of duration and intensity in any satisfactory way. The additional difficulties arising from misclassification of smoking status or ETS exposure have been amply described in the literature. The erroneous classi-

fication of actual smokers or former smokers as nonsmokers would have serious consequences on epidemiologic results, especially because smokers tend to be married to smokers. The National Research Council Committee on Passive Smoking outlined the knowledge that would be necessary to assess the impact of classification bias, namely, the proportion of the sample that was misclassified, the proportion of male and female subjects, the proportion of married couples that have the same smoking habits, and the relative lung cancer risk of misclassified smokers and nonsmokers (NRC, 1986). Although it is self-evident that knowing all this would eliminate classification bias, these variables have not been measured or reported in studies and therefore are subject to conjectures and assumptions that, however educated, have led to very different assessments (NRC, 1986; Lee, 1987a). In this regard it is possible to state only that misclassification bias is difficult to assess but very probable, and its impact could be of sufficient magnitude to explain the marginal lung cancer RRs reported by some ETS studies (Lee, 1987b).

An even greater prejudice to the credibility of ETS epidemiologic studies derives from their failure to account and control for the possible confounding by many independent risk factors. For lung cancer, a selected list of these is given in Table 6.

Since many of the RRs in Table 4 are substantially larger than any reported for the association of lung cancer and ETS, even weak contributions by combinations of these confounders would be cumulative and could be more than sufficient to explain the marginal lung cancer risks that some epidemiologic studies of ETS have reported. In fact it is likely to be so, because these studies have not controlled for the factors of Table 4 in any meaningful or comprehensive way, while other investigations provide evidence that several of those risk factors cluster and selectively segregate in families with smokers (Subar *et al.*, 1990; Morabia and Wynder, 1990; Sidney *et al.*, 1989; Whichelow *et al.*, 1988, 1991; Koo *et al.*, 1988; Pisani *et al.*, 1986; Friedman *et al.*, 1983). For cardiovascular diseases the independent risk factors reported in the literature number over 200, many of which are the same as apparent lung cancer risks (Hopkins and Williams, 1981). For respiratory diseases analogous independent risk factors have been identified, ranging from genetic to sociologic, to dietary and environmental conditions, also likely to cluster in households with smokers (Shilling *et al.*, 1977; Comstock *et al.*, 1981; Morris *et al.*, 1990; Schwartz and Weiss, 1990).

It should be clear that the seemingly insurmountable difficulties in measuring ETS exposures and doses, unresolved classification bias, and the inability to control for numerous independent confounders explain the inconsistency of weak ETS epidemiologic results and speak against scientifically credible conclusions about a risk that, if real at all, remains imponderable.

Indeed, the only justifiable conclusion is that this issue cannot be resolved scientifically on the basis of currently available information. Moreover, exposure and dose considerations alone seem to indicate that ETS is an insignificant entity among the substantial mass of exogenous and endogenous challenges to health that we continually face.

Hypothetical risks from feeble ETS exposures have been postulated only by presuming what is merely possible, even if extremely unlikely, as opposed to what is scientifically demonstrable and probable. Although at times politically tempting, such hypothetical presumptions are not science and should be resisted. If accepted, they are likely to foster irrational fears, not the enlightened prudence that responsible public health policy should cultivate.

TABLE 6

REPORTED INDEPENDENT RISK FACTORS FOR LUNG CANCER

Factor	Reference	Maximum RR reported	95% CI
Family history of lung cancer	Samet *et al.* (1986)	5.3	(2.2–12.8)
	Ooi *et al.* (1986)	2.4	
	Horwitz *et al.* (1988)	2.8	(1.0–7.7)
	Wu *et al.* (1988)	3.9	(2.0–7.6)
Family history of tuberculosis	Wu *et al.* 1988)	10.0	(1.1–90.1)
	Sakurai *et al.* (1989)	6.4	
	Gao *et al.* (1987)	1.7	(1.1–2.4)
	Hinds *et al.* (1982)	8.2	(1.3–54.4)
β-carotene/vitamin A deficiency	Byers *et al.* (1987)	0.3	(P = 0.06 trend)
	Pastorino *et al.* (1987)	0.2	
	Wu *et al.* (1985)	0.4	(0.2–0.9)
	Ziegler *et al.* (1986)	2.2	
Alcohol intake	Pollack *et al.* (1984)	2.19	(1.3–5.0)
Dietary cholesterol/fat	Goodman *et al.* (1988)	2.2	(1.3–3.8)
Dietary fat intake	Wynder *et al.* (1987)	4–6	
Pork meat intake	Mettlin (1989)	2.4	(1.4–4.2)
Vegetable diet	Jain *et al.* (1990)	0.6	(0.4–0.88)
	Le Marchand *et al.* (1989)	0.3	(P = 0.009 trend)
Fruit intake	Koo (1988)	0.4	(0.2–0.9)
Milk intake	Mettlin (1989); Mettlin *et al.* (1990)	2.1	(1.4–3.2)
Hormone therapy in women	Adami *et al.* (1989)	1.3	
Cooking methods	Gao *et al.* (1987)	1.4–2.6	(1.1–5.0)
	Geng *et al.* (1988)	5.6	(3.4–9.1)
	Sobue *et al.* (1990)	1.9	(1.1–3.3)
	Mumford *et al.* (1987)	2–3	
Radon	Edlin *et al.* (1984)	4.3	(1.7–10.6)
	Lees *et al.* (1987)	2.4	(0.8–7.1)
Occupation	Kvale *et al.* (1986)	2.6	
Motor exhaust exposure	Hayes *et al.* (1989)	1.5	(1.2–1.9)
Socioeconomic class	Brown *et al.* (1975)	2.6–3.8	
Ventilatory function	Lange *et al.* (1990)	2–4	
Cardiac anomalies	Tenkanen *et al.* (1987)	2.4	
Physical inactivity	Albanes *et al.* (1989)	1.6	(1.2–3.5)
	Severson *et al.* (1989)	1.4	(1.0–2.1)
Psychosocial traits	Kulessa *et al.* (1989)	2–3	
Urban/rural risk ratio	Shy (1984)	1.2–2.8	

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REVIEW ARTICLE

Environmental Tobacco Smoke: Current Assessment and Future Directions*

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Abstract

Scientific information on environmental tobacco smoke (ETS) is critically reviewed. Key areas addressed are: differences in chemical composition between mainstream smoke, sidestream smoke, and ETS; techniques for measurement of ETS; epidemiology; *in vitro* and *in vivo* toxicology; and chamber and field studies of perceptual or physiological effects. Questions concerning estimation of ETS exposure, suitability of various biomarkers, calculation of lifetime dose, control of confounding variables, use of meta-analysis, and the relationship between ETS concentrations and human responses all emphasize the need for additional research in order to assess potential effects of ETS on health or comfort.

Keywords. Smoke chemistry; epidemiology; toxicology; sensory; measurement techniques; environmental tobacco smoke (ETS)

Introduction

Reports that nonsmokers experience acute and chronic health effects from tobacco smoke are relatively recent additions to the scientific literature. Reported acute effects include upper airway reactions as well as perceived odor and irritation. Epidemiology studies have reported associations between exposure to environmental tobacco smoke (ETS) and lung cancer, cardiovascular disease (CVD), and other respiratory diseases. In addition, a limited number of studies have been conducted on animals exposed to surrogate aerosols of ETS.

In 1980, White and Froeb (148) concluded that nonsmokers who were exposed to tobacco smoke in the workplace had significantly reduced small-airway function. In 1981, it was reported in 2 articles (63, 136) that nonsmoking wives of smokers were at increased risk of developing lung cancer. Studies reporting respiratory symptoms and assessing pulmonary function of children in smoking households date from the 1970s (27, 80, 122, 131). The first reports of studies to assess the relationship between exposure to tobacco smoke and cardiovascular disease in nonsmokers appeared in the 1970s (2, 70, 115).

The scientific literature on ETS has grown rapidly and today comprises thousands of articles. Reviews and assessments of these publications are also numerous, both in the US and internationally (33, 52, 72, 101, 138). Two reports produced in 1986 under federal government sponsorship concluded that ETS causes nonsmokers to have increased risk of lung cancer and increases respiratory infections and symptoms in children of smokers (101, 138). More recently, the Environmental Protection Agency issued a draft report estimating that 3,800 US lung cancer deaths per year are attributable to ETS (139).

Most of the research reported to date concerning ETS and health effects is from epidemiology studies. These individual epidemiology studies, however, have not provided a clear picture of relative risks associated with ETS exposure. The results are often inconsistent, and where there are reports of associations, those associations are very weak. Consequently, a variety of techniques, including meta-

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TABLE I.—Diet and lung cancer risk.

Study	Dietary factor	Relative risk/odds ratio*
Fraser et al (44)	Low fruit consumption	3.83, $p = 0.0003$
Sakai (117)	Consuming the aloe plant	0.5, $p < 0.1$
Mettlin (98)	Consumption of whole milk	2.14
	Consumption of low-fat milk	0.54
Hole et al (66)	Low cholesterol level	Increased risk in those who smoke >15 cigarettes per day.
Connett et al (28)	Low serum beta-carotene	2.32
Marchand et al (91)	Low beta-carotene intake (men)	1.9 (95% C.I. 1.1–3.2)
	Low beta-carotene intake (women)	2.7 (95% C.I. 1.2–6.1)
Kune et al (78)	Serum beta-carotene Serum vitamin A	Patients had significantly lower levels than controls.
Koo (76)	Low fruit consumption	2.4, $p < 0.002$
	Low fish consumption	2.8, $p < 0.017$
Goodman et al (50)	High intake of cholesterol and fat	2.2 (95% C.I. 1.3–3.8) for men only
Pastorino et al (110)	Low plasma retinol	1.13
	Low retinol intake	3.27
	Low plasma beta-carotene	5.04
	Low beta-carotene intake	2.93
Bond et al (12)	Low vitamin A intake	2.0
Byers et al (16)	Low dietary fat intake	0.5
	Low fruit and vegetable consumption	1.8
Wynder et al (151)	Calories from dietary fat (by country)	Highly significant positive association ($p < 0.0001$) with national lung cancer mortality rate.
Menkes et al (97)	Low serum beta-carotene	4.30 (95% C.I. 1.38–13.41)
	Low serum vitamin E	2.5 ($p = 0.04$)
Pisani et al (112)	Low carrot consumption	2.9, $p < 0.01$ for current smokers
Chrisley et al (23)	Low vitamin B-6 level	All 12 cancer patients and none of the control subjects had vitamin B-6 inadequacy.
Ziegler et al (155)	Low carotene intake	1.4 (p-value for trend = 0.03) for squamous cell carcinoma.
Hinds et al (62)	Low vitamin A intake	2.0 (95% C.I. 1.2–3.5)
	Low carotene intake	2.2 (95% C.I. 1.3–3.7)
Byers et al (15)	High vitamin A intake	0.73 for squamous cell carcinoma

* For a complete description of the calculation of relative risks and odds ratios see Feinstein (39).

analysis, have been employed to evaluate these studies as a whole, in an attempt to provide greater statistical confidence in the findings.

This report briefly examines some of the difficulties in analyzing and interpreting the scientific literature on ETS and offers suggestions to overcome some of these limitations. In particular, it explores the following considerations:

1) In studying the hypothesis of an association between ETS exposure and the development of chronic disease, it is particularly difficult to account for confounding risk factors and the relative contribution of these factors.

Epidemiological studies of associations between ETS exposure and adult chronic disease have typically used the smoking status of household members as the index of exposure. The reported relative risks or odds ratios have generally been no larger than 2.0, approximately the same magnitude as confounding lifestyle factors (Tables I–IV). In addition, there is evidence that many of these confounders are non-symmetrically distributed between smoking and nonsmoking households (see Epidemiology section).

2) Significant chemical, physical, and physiological differences (e.g., component phase distribution, particle size, concentration, and inhalation/deposition patterns) between ETS, mainstream (MS) cigarette smoke, and freshly generated sidestream (SS) smoke preclude using MS or SS as simple surrogates for ETS. These differences also make evidence from studies exploring the effects of active smoking of limited value in drawing conclusions about ETS (51, 53).

3) Lifetime ETS dosimetry in a given nonsmoker is difficult to determine.

4) There is general agreement that meta-analytical techniques should follow certain established guidelines to increase confidence in the results. The lack of homogeneity within the reported ETS epidemiological studies renders meta-analysis problematic.

5) Sensory irritation associated with exaggerated ETS concentrations (10–100 times that found in field studies) does not provide a basis for drawing conclusions about the sensory effects of ETS at real world concentrations.

QUANTITATIVE DIFFERENCES BETWEEN ETS AND MS SMOKE

Laboratory research on ETS has been limited by the use of surrogate aerosols that are likely to have

TABLE II.—Occupation and lung cancer risk.

Occupational exposure	Study	Relative risk/odds ratio
Welders	Breslow et al (13)	7.7
	Lerchen et al (84)	3.2 (95% C.I. 1.4–7.4)
	Buiatti et al (14)	2.8
	Tola et al (135)	7 observed, 2 expected ($p < 0.01$)
	Hull et al (68)	1.7 ($p < 0.05$)
Painters	Lerchen et al (84)	2.7 (95% C.I. 0.8–8.9)
	Engholm et al (37)	1.26
Painters, plasterers, and wallpaper hangers	Zahm et al (154)	2.0 (95% C.I. 1.2–3.3)
Farmers	McDuffie et al (95)	"Patients were consistently exposed more frequently to herbicides ($p = .05$), grains ($p < .015$), and diesel fuels ($p < .005$), and were consistently exposed to greater numbers of chemicals than were siblings ($p < .005$)."
Pesticide applicators	Vineis et al (140)	2.1 (95% C.I. 0.5–8.5)
Railroad workers exposed to diesel exhaust	Garshick et al (46)	1.45 (95% C.I. 1.11–1.89)
Chlorinated toluene workers	Sorahan and Cathcart (127)	1.80 ($p < 0.05$)
Chloromethyl ether workers	Maher and DeFonso (88)	2.79 ($p < 0.01$)
Steel workers exposed to acid mists	Beaumont et al (8)	2.00 (95% C.I. 1.06–3.78)
Pottery workers exposed to silica and talc	Thomas and Stewart (133)	3.64 among those exposed for 15 or more years.
Ceramic workers exposed to silica	Forastiere et al (43)	2.0 (95% C.I. 1.1–3.5)
Brick plant workers exposed to silica	Puntoni et al (114)	1.83
Asbestos	Sluis-Cremer and Bezuidenhout (126)	3.75
New Mexico uranium miners	Samet et al (120)	4.1 (95% C.I. 3.2–5.2)
Indoor radon	Samet (119)	"Estimates of the lung cancer risk associated with average lifetime radon exposure range from 0.1% to 1.0%."

different biological activities than ETS. A clear distinction should be made between mainstream (MS) cigarette smoke, sidestream (SS) smoke, and ETS.

ETS is the aged, diluted mixture of exhaled MS smoke and SS smoke. MS smoke, SS smoke, and ETS are largely composed of the same chemical compounds (4, 6, 35). However, because ETS is a highly diluted, dynamic mixture, it differs greatly from MS smoke and SS smoke in concentration, phase distribution, and component particle size (6, 51, 105).

The differences in phase distribution primarily result from 2 factors: the dilution (approximately 100–1,000 times) of ETS components, and differences in pH between MS smoke (below 7.0) and SS smoke (above 7.0). These physicochemical differences affect the volatility and phase transfer properties of ETS components.

The high degree of ETS dilution can be seen by comparing the concentration of individual MS components to the concentration of the same ETS components. These differences can approach 3 orders of magnitude (Table V).

In addition to phase and concentration differences, particle size differences between ETS, MS smoke, and SS smoke affect the bioavailability and therefore the biological activity of smoke components.

Relative humidity in the human respiratory tract approaches 100% (40, 51). In this environment, particles of freshly generated MS smoke increase in size because of coagulation and water acquisition. When exhaled, these enlarged particles (20–25% larger than the inhaled particles) almost immediately lose water and other volatile components to the atmosphere by evaporation. As a result, their size decreases.

TABLE III.—Genetic factors and lung cancer risk.

Genetic factor	Study	Relative risk/odds ratio
Family history	Tokuhata and Lilienfeld (134)	2.7
	Ooi et al (108)	2.4
	Samet et al (118)	5.3
	McDuffie et al (96)	2.0
Rapid metabolism of the drug Debrisoquine	Ayesh et al (5)	4.5
	Caporaso et al (19)	

TABLE IV.—Poor lung function as a lung cancer risk factor.

Study	Risk factor
Kuller et al (77)	"Smokers in the lowest quintile of forced expiratory volume in one second (FEV_1) were seven times more likely to die of lung cancer than those in the highest two quintiles, $P \leq 0.001$ for linear trend."
Cohen et al (26)	After adjustment for age, sex, race, and smoking, the first-degree relatives of lung-cancer patients and of patients with chronic obstructive pulmonary disease were found to have significantly higher rates of impaired forced expiration than first-degree relatives of patients with non-pulmonary disease.
Guirgis et al (54)	These authors observed an increased frequency of pulmonary diseases in the relatives of lung cancer patients.

Note—peak lung function at maturity can be influenced by many factors, including: genetics, childhood respiratory infection, diet, exercise, premature birth, history of adult lung disease (pneumonia, tuberculosis), and environmental exposures.

Similarly, freshly generated SS particles—originally about the same size as freshly generated MS particles—also diminish in size as they lose volatile components, including nicotine, to the atmosphere. Through these evaporative processes, the mass mean aerodynamic diameter of SS particles formed during smolder is reduced 40–50% (71).

Measurements in active smokers have reported MS particle phase retentions ranging from 40% to 90% (61). When measured experimentally, ETS particle retention was found to be 11% (60).

MEASUREMENT TECHNIQUES FOR ETS

Accurately measuring ETS exposure is problematic. Various techniques have been evaluated and employed to measure ETS in an attempt to overcome the general difficulty of measuring minute concentrations of individual components in complex mixtures.

Chemical and biological estimates of ETS exposure have been reported. The most widely utilized chemical markers of ETS are nicotine and respirable suspended particulates (RSP). These components have been used to represent the vapor and particulate phases, respectively, of the ETS aerosol. Airborne nicotine, however, does not maintain a constant ratio to other vapor phase components (102). Furthermore, isolating ETS as a source of RSP is mitigated by the fact that other sources of particles are usually present. ETS typically contributes less than half of the total particles in indoor environments where smoking is allowed (34, 106, 113). Better chemical markers for ETS particle phase exposure that are under development include solanesol

TABLE V.—Dilution factors: MS components inhaled by a smoker versus ETS components inhaled by a nonsmoker breathing ETS-containing indoor air.

Tobacco smoke component	MS/ETS dilution factor
Nicotine	57,333–7,200,000
Acrolein	1,500–20,833
Benzene	112–7,167
Acetone	240–2,000
Benzo(a)pyrene	68–40,740

Data are taken from National Research Council data (101).

and ultraviolet particulate matter (106). 3-Ethenylpyridine is being investigated as a more precise indicator of vapor phase components (103).

Biological markers that have been used to monitor exposure to ETS include carboxyhemoglobin in blood; urinary mutagenicity, as measured by the *Salmonella* assay; and concentrations of nicotine and a major metabolite, cotinine, in blood, urine, and saliva (56). In 1984, Matsukura et al (93) reported that cotinine could be used to indicate nonsmoker exposure to ETS. In 1989, Curvall (30) reported the use of trans-3'-hydroxycotinine as a more reliable indicator of ETS exposure than cotinine, but neither nicotine nor its metabolites can be used to quantitatively assess ETS exposure (104).

Further research is underway to establish biomarkers that are specific to tobacco smoke, reproducible, and proportional to the original concentration of ETS as a function of time. Currently, there are no accurate measures available to either chemically or biologically quantify ETS exposure.

EPIDEMIOLOGY

A number of challenges remain in order to perform reliable epidemiological studies of the potential association between ETS exposure and the development of chronic disease. These include improvements in lifetime dosimetry estimates and in adjustments for potential confounders.

Determining Lifetime ETS Exposure

A reliable lifetime exposure estimate is essential in studying the potential association between any compound and chronic disease. With the exception of certain acute respiratory conditions, the diseases that have been reported to be associated with ETS exposure are of a chronic nature and develop over a period of many years.

Several technical problems make estimates of lifetime ETS dosimetry difficult: 1) Current exposure is not necessarily a good indicator of past exposure. 2) Self-administered questionnaire and interview data are generally less reliable than biochemical measures of exposure. 3) Estimates of household

exposure or workplace exposure do not consider other potential sources (e.g., bars, restaurants, etc.) of exposure that would alter the total dose.

Although it would be very difficult to overcome these technical problems in any epidemiological study, suggestions to partially address these difficulties include: 1) Analytical measurements of ambient ETS concentration should be taken in both the homes and the workplaces of cases and controls. 2) A reliable biological marker of ETS exposure should be measured from fluid or tissue samples taken from the subjects to confirm exposure. 3) Subjects should be interviewed, whenever possible, because data on past exposure are more reliable when collected by trained interviewers than by self-administered questionnaire (55, 87, 121). If the subject is not available, the subject's spouse is the relative of choice to interview.

Adjusting for Potential Confounders

Because the relative risks or odds ratios for human diseases reported to be associated with ETS exposure are typically no larger than the risks for confounding lifestyle factors, epidemiological studies of the association between exposure to ETS and chronic disease should be designed to maximize data quality and statistical power.

Several investigators have reported that smokers as a group have life-styles that put them at greater risk for chronic disease than nonsmokers, independent of smoking (36, 79, 124, 147). The life-styles of families of smokers and families of nonsmokers also differ. In 1987, Perusse et al (111) demonstrated familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. In 1989, Myers et al (100) reported results from the Framingham Study suggesting that there is a familial similarity in lipoprotein cholesterol levels.

Other authors have reported significant dietary differences between the families of smokers and the families of nonsmokers. Sidney et al (125) observed that the self-reported dietary intake of carotene is lower in nonsmokers exposed to ETS at home than in nonsmokers not exposed to ETS at home. These authors also found a higher proportion of current alcohol consumers and slightly higher mean body mass index in the exposed subgroup, despite its considerably lower age.

The ETS and chronic disease epidemiology studies conducted to date have not adequately controlled for all of the known confounding variables. When interpreting these studies, Angell's caveat (3) should be noted—"although there are statistical methods for neutralizing confounding variables, they are not perfect, and they are of no use whatsoever unless the confounding variables are known and measured."

ETS and Lung Cancer

At least 31 spousal studies have compared the risk of lung cancer in nonsmoking spouses of smokers to the risk in nonsmoking spouses of nonsmokers. These studies reported relative risks ranging from 0.7 to 2.55. Twenty-five of the studies reported no statistically significant increase in risk. On average, the 6 studies reporting an increase show an association generally less than 2.0 between spousal smoking status and lung cancer.

Although epidemiology studies do not establish causal relationships, the spousal studies do not make clear whether the reported associations are indicators of risk of ETS exposure, indicators of risk of spousal smoking status, or methodological artifacts. Because of inherent difficulties in interpreting any weak epidemiologic association and specific difficulties with the spousal studies, ETS/lung cancer epidemiology studies should contain the following elements: 1) Histological confirmation by a pathologist that the reported lung cancer cases are primary lung cancers. 2) Histological categorization of the primary lung cancer. 3) A "best estimate" of lifetime ETS exposure in cases and controls, taking into account factors mentioned earlier. 4) Demographic information concerning age, gender, ethnic origin, body mass index, etc. 5) Reliable estimates of the following reported lung cancer risk factors for both cases and controls: genetic predisposition as measured by family medical histories, air pollution, occupational carcinogens, long-term dietary habits, and peak lung function at maturity, exercise habits, prior lung disease (Tables I–IV).

ETS and Cardiovascular Disease (CVD)

To date, at least 10 epidemiology studies have examined the association between ETS and heart disease. Of the 4 studies conducted on men married to women who smoke, 3 (47, 83, 130) have 95% confidence intervals that go below 1.0. The 95% confidence interval of the fourth study (59) has a lower limit value of 1.1.

Of the 8 studies conducted on women married to men who smoke, 5 (45, 47, 64, 69, 83) have 95% confidence limits that either include or go below 1.0. The 95% confidence intervals of the other 3 studies approach 1.0, with lower limit values of 1.1 (59), 1.2 (92), and 1.3 (57). The 1 study that combined men and women (65) reported a 95% confidence interval with a lower limit of 1.2. All of these studies are either statistically insignificant at the 95% level or have lower limit values that approach 1.0.

Three studies (45, 47, 130) have reported positive

associations (that were not significant at the 95% level) between exposure to ETS and CVD that are stronger than CVD risks reported in cigarette smokers (137). This anomalous result may suggest methodological problems with these studies.

Future biochemical epidemiology studies on exposure to ETS and cardiovascular disease should place greater emphasis on atherothrombotic, rather than just atherogenic, endpoints. Some degree of atherosclerosis is prevalent in males in Western societies, and atherothrombotic endpoints can be measured from blood samples and can be followed sequentially. Relevant atherothrombotic endpoints of interest in an ETS exposure study should include total peripheral white blood cell count, fibrinogen level, and possible indicators of platelet aggregation (32, 38, 74, 132).

Platelet aggregation has often been cited as a potential atherothrombotic event (74). The presence or absence of platelet aggregation after cigarette smoking can be experimentally determined, but its biological significance remains controversial. In addition, measurements of prostacyclin and thromboxane do not address whether the platelets of chronically smoke-exposed individuals are tolerant to chemical stimulators of aggregation.

ETS and Respiratory Health in Children

Hood et al (67) recently reviewed the epidemiological literature on ETS exposure and respiratory health in children. These authors stated:

> There appears to be a consistent association between parental (primarily maternal) smoking and respiratory symptoms and certain diseases in preschool children (44 reports). On the other hand, there is no consistent association between parental smoking and (1) respiratory symptoms or disease (46 reports); (2) middle ear disease (17 reports), (3) pulmonary function (38 reports), or (4) lung growth and development (5 reports) in school-age or older children.

An epidemiological association between ETS exposure and respiratory disease endpoints in children is difficult to determine because there are many possible factors in early lung impairment. Some factors that should be controlled in such an ETS epidemiology study include (94): 1) Mechanical trauma and hyperoxia on the premature lung (bronchopulmonary dysplasia). 2) Lung restriction that retards lung growth (pectus excavatum, congenital diaphragmatic hernia, congenital lobar emphysema). 3) Hypoxia that retards the subsequent structural and functional development of the pulmonary vasculature. 4) Airway inflammation in infancy that reduces subsequent airway function. 5) Maternal malnutrition or poor prenatal care during pregnancy. 6) Malnutrition during periods of rapid lung growth during infancy and early childhood.

In addition, such infectious exposures as measles, pertussis, adenovirus, etc., should also be determined in both the controls and the cohort under study. No study conducted to date has controlled for all of these risk factors.

As with lung cancer and heart disease, the differences in life-style between the families of smokers and the families of nonsmokers necessitate the consideration of potential confounders when investigating childhood respiratory disease. The socioeconomic status of the household and cross-infections from parents and siblings are particularly difficult to disentangle in these studies of acute effects.

ETS and Respiratory Health in Adults

Respiratory diseases and symptoms in either healthy or compromised adults exposed to ETS have not been as widely studied as in children. No clear picture emerges from an analysis of the approximately 40 published papers on this subject, because the literature reports positive and negative associations as well as nonassociations.

The ETS studies on adult respiratory health are influenced by many of the same potential confounders as the childhood studies, but there are at least 5 factors that may be of increased importance in considering design of ETS studies in adult populations: 1) Presence of adult lifestyle confounders (e.g., alcohol consumption, caffeine consumption, hobbies such as woodworking and ceramics, etc.). 2) Occupational exposures to lung irritants. 3) Difficulty in obtaining accurate lifetime medical histories. 4) Greater difficulty in estimating current and past ETS exposure because of the increased mobility of adults. 5) Increased possibility of psychological aversion to ETS, resulting in exacerbation of reported symptoms.

In vitro Studies on ETS

In vitro techniques have been used for many years to assess the mutagenicity and cytotoxicity of compounds and complex mixtures. There may be no consistent correlation between the carcinogenicity of a chemical compound in animal tests and positive genotoxic or cytotoxic *in vitro* results (1). Nonetheless, valuable mechanistic information can sometimes be obtained from the results of these tests.

Recently, the biological activity of ETS was assessed using a cellular smoke exposure technique that utilized exposures to ETS of 1.5 mg/m^3, approximately a 15-fold increase over real-life measured levels of RSP, of which ETS comprises at most 50% (11). Effects of this ETS concentration were

compared to those of room air. ETS was not cytotoxic (neutral red assay), mutagenic (Ames tests using the TA98 strain with S9 metabolic activation) or clastogenic (sister chromatid exchanges).

Animal Studies on ETS

Several nose-only inhalation exposure studies of MS smoke have reported histopathological changes of the respiratory tract and related organs in several species.

A 14-day inhalation study in rats was recently conducted to determine whether ETS would produce similar results (24). This study used SS smoke that was aged and diluted (ADSS) to closely approximate the phase distribution and concentrations of ETS components. Animals were exposed nose-only, inside whole-body chambers, to ADSS from the 1R4F reference cigarette. Endpoints included histopathology, CO-oximetry, plasma nicotine and cotinine, clinical pathology, and organ and body weights. The only pathological response observed was slight to mild epithelial hyperplasia and inflammation in the most rostral part of the nasal cavity, in the high exposure (100 × "real-life") group only. No effects were noted at medium (10 ×) or low (1 ×) exposures. The minimal changes noted were reversible.

A 90-day study by Coggins et al (25) using the same ADSS concentrations produced similar results, with no histopathological progression noted. In addition, no new histopathological changes were observed at 90 days. These results are in agreement with von Meyerinck et al (141), who conducted a 90-day SS smoke study on rats and hamsters utilizing an exposure of 4.0 mg/m^3 in which the only histopathological changes observed were reversible hyperplasia and metaplasia of the epithelium covering the dorsal nasal turbinates in the rats.

Lee et al (81) examined DNA adducts and alveolar macrophage cytogenetics in the rats from the 14-day inhalation study conducted by Coggins et al (24). Exposure-related adducts were not observed in any of the animals at 0.1 or 1.0 mg/m^3; these figures represent ambient and a 10-fold exaggeration for measured ETS concentrations, respectively. Slight diagonal radioactive zones, characteristic of adducts observed in animals in smoke exposure studies, were observed, but only in lung and heart DNA of animals exposed to the highest concentration of ADSS (10 mg/m^3), a 100-fold exaggeration of typical field measurements of ETS. No elevation in chromosomal aberrations was observed in the alveolar macrophages. These results are consistent with the histopathology data in support of a no-observed-effect-level (NOEL) of 1.0 mg/m^3.

Meta-Analysis

Meta-analysis is a collection of statistical procedures for combining and analyzing data from "similar" studies. It is contrasted with primary analysis (the original analysis of data from a single study) and secondary analysis (the re-analysis of original data by a different technique, for another purpose or by another investigator) (48).

Most often, meta-analysis operates on summary statistics of primary studies—correlation coefficients, p-values, relative risks, or contingency tables—as opposed to a pooled compilation of raw data from individual studies (58). Meta-analysis is almost exclusively applied to derive a single consolidating statistic that represents the significance of an intervention effect (e.g., symptom remediation under a prescribed treatment regimen) or to derive a relative risk for exposure to a particular agent (128).

Sacks et al (116) have cited the following objectives of meta-analysis: 1) to increase statistical power for primary endpoints and for subgroups, 2) to resolve uncertainty when reports disagree, 3) to improve estimates of effect size, 4) to answer questions not posed at the start of individual trials.

Several researchers have provided guidelines for proper application of meta-analytic techniques (10, 22, 42, 73, 109, 116, 152, 153). The guidelines of Sacks et al (116), as presented by Fleiss and Gross (42), are paraphrased below:

Study Design

The design of the meta-analysis should include a protocol prepared before study initiation. The protocol should describe the purpose of the meta-analysis, the methods for obtaining published data, a list of all studies found, criteria for exclusion of studies not pooled in the meta-analysis, and summary data on clinical and demographic characteristics in the studies.

Combinability

Researchers should report their criteria for whether individual studies are sufficiently "similar" to be combined. This includes the calculation of a statistical homogeneity/heterogeneity index.

Control and Measurement of Potential Bias

One important potential source of bias in meta-analysis is the selection of the studies that are included. Selection or rejection should be based on the methodology of the studies (not on their results). Bias may also arise in extracting data from individual studies. To minimize "extraction bias," 2 or more investigators should independently review the studies and attempt to reach consensus. Sources of

funding for the meta-analysis should also be identified.

Statistical Analysis

An appropriate statistic for averaging "within-study" differences (analysis of variance or Mantel-Haenszel) should be employed. Point and interval estimates, in addition to overall significance tests, should be reported. The question of statistical power should be addressed, especially when a weak or insignificant association is predicted by the meta-analysis. Subgroup associations hypothesized *a priori* should be meta-analyzed (i.e., the decision to study specific subgroups should be made before the results of the full meta-analysis are known).

Sensitivity Analysis

Studies should be analyzed in more than 1 way (different statistical tests, assumptions, or criteria) to confirm qualitative agreement. The potential impact of publication bias (the rejection by publishers of studies that fail to show an effect) and "the file-drawer phenomenon" (the tendency of authors to not submit for publication studies that fail to show an effect) should be carefully assessed. The quality of the individual studies should be assessed (weighted) and incorporated in the final conclusions.

Application of Results

Once the pooled statistics have been obtained, the investigators should carefully evaluate the results for procedural rigor and overall validity, questioning whether a definitive answer has been provided, or whether further studies are needed.

Some authors have also emphasized the following: 1) the importance of including only randomized studies in a meta-analysis (153), 2) the value of displaying data graphically (10, 42), 3) the importance of searching both the published (peer-reviewed) and unpublished (theses, regulatory documents, etc.) literature for data (10, 153). In addition, the quality of the meta-analysis cannot exceed the quality of the component data sets.

Meta-analysis has recently been applied to the epidemiology of lung cancer in relation to ETS (9, 42, 85, 86, 101, 139, 142, 146). These meta-analyses were based on a variety of assumptions and corrections, and they used different protocols, subject populations (overlapping to various extents), and meta-analytic tools.

All meta-analyses found summary risk ratios less than 2.0 (most less than 1.5) for nonsmoking women married to smokers. All meta-analyses used at least 1 of the 2 procedures developed by Mantel and Haenszel (90) or Yusuf et al (153). Letzel and Uberla (86) used both procedures, in addition to Fisher's p-value method (41).

The meta-analyses of the National Research Council (NRC) (101), the Environmental Protection Agency (EPA) (139), Wald et al (142), Wells (146) and Blot and Fraumeni (9) predicted lower 95% confidence limits above unity, indicating statistical significance for increased risk. The lower confidence limits of Letzel et al (85) and Fleiss and Gross (42) were below unity, indicating nonsignificantly increased risk.

All relative risks calculated were small (150). The fragility of such small increased risks (89) indicates the need for statistical power analyses and further epidemiology (42).

Many questions remain about meta-analytic theory and application (21, 42, 49, 116, 128). Most practitioners of meta-analysis question the propriety of combining studies of widely variable study populations, methodologies and controls.

Among the more important questions raised by meta-analysis of ETS studies are how to account for variances in the quality and size of component data sets, how to correct for publication bias, how to account for potentially confounding variables in the individual and overall statistics (42), and how to assess the overall homogeneity/heterogeneity of studies.

Misclassification bias has also been suggested as a potential source of error in ETS epidemiology (82). Finally, Fleiss and Gross (42) stress the need for data adjustment for misclassification of case-control status and exposure level.

SHORT-TERM EFFECTS OF ETS EXPOSURE

Background

ETS may have both perceptual and reflexive effects in nonsmokers. Nonsmokers may perceive odor, nasal irritation, and eye irritation; in some cases, they may also see ETS. Reflexive responses that have at least been anecdotally associated with ETS include increased eye blinking, tearing, runny nose, cough, headache, and upper airway changes such as bronchoconstriction. All of these effects are influenced by both the smoke concentration and individual differences in sensitivity to ETS.

Although information on the prevalence of any of these effects in work or any other environment is scant, some laboratory experiments on responses to ETS have been reported. These can be divided into those that emphasize perceptual effects and those that deal primarily with physiological or pharmacological measurements of upper airway function.

Perceptual Studies

In a number of studies reported in the past 10–12 years, ratings of odor and irritation were measured over ranges of concentrations of true ETS or

machine-generated SS smoke. In several of these studies, the nonsmokers were also asked to rate the annoyance from, or acceptability of, chamber air after smoke was produced. Most often, carbon monoxide (CO) concentrations were used as a measure of smoke concentration. Estimates of the smoke concentrations used in these studies, relative to those found in actual smoking environments, may be made by comparing the average nicotine and RSP concentrations reported in a series of recent field-sampling studies (20, 29, 107) with those measured in a recent laboratory study (143). This comparison indicates that ETS concentrations corresponding to elevations of ~0.15–0.30 ppm CO might be representative of office and restaurant smoking environments. Because all reports of the perception of ETS employed concentrations much higher than this, these studies provide an incomplete understanding of the perceptual effects from environmentally realistic exposures. Nonetheless, several findings from this line of research are worthy of note:

1) With combinations of smoking and ventilation rates that result in CO concentrations of 2 ppm or lower, 90% of chamber occupants report being satisfied with the air; at 5 ppm CO, satisfaction declines to 75% (18).

2) Filtration to remove particulate matter from SS smoke at 10 ppm CO greatly reduces ratings of perceived eye or nasal irritation (144). Relatively smaller declines in odor and irritation were seen with particulate matter removal at lower (2 and 5 ppm CO) concentrations of ETS (18).

3) Eye blink rate and changes in respiratory behavior are of little value as physiological correlates of perceived irritation in nonsmokers exposed to environmentally realistic levels of ETS. Both measures are largely unaffected unless concentrations at least 20-fold higher than real world levels are employed (75, 99, 143–145).

4) Prolonged exposure (at least 30 minutes) to constant ETS concentrations of 1.3–10 ppm CO results in gradual increases in perceived eye and nasal irritation (18, 99).

5) The single most sensitive measure of ETS annoyance, particularly at lower concentrations, is odor. There is some evidence that the intensity, rather than the quality, of the odor is the more important determinant of nonsmokers' annoyance (17).

The research by Cain et al (17, 18) that indicated a key role of odor in ETS complaints, employed ETS concentrations in the range of 2–5 ppm CO. When lower concentrations, more closely approximating those in office smoking environments, are presented in future studies, one would expect the relative importance of odor to increase substantially. Considerations of the meaning of nasal or eye irritation ratings should await the collection of data at these lower concentrations. Ideally, future studies in this area should also determine the ETS concentration thresholds for odor, irritation, and more "global" measures such as annoyance or acceptability.

Studies of Upper Respiratory Reactions to ETS

Attempts to produce asthmatic responses or other changes in upper airway function in nonsmokers have used concentrations of machine-generated SS smoke in the range of 8.7 (129) to 50 (149) ppm CO and have produced equivocal results. In 14 asthmatics (4 of whom reported that ETS aggravated their symptoms), SS smoke concentrations of approximately 24 ppm CO did not alter forced expiratory volume in 1 second (FEV_1) or maximal expiratory flow rate at 50% of vital capacity ($\dot{V}max50$) (123). Wiedemann et al (149) exposed 9 asthmatics (6 of whom reported that ETS "bothered" their asthma) to SS smoke concentrations corresponding to 40–50 ppm CO. These exposures did not result in changes in FEV_1 or $\dot{V}max50$, but they did produce a 2% decrease in forced vital capacity (FVC). A slight *decrease* in nonspecific bronchial reactivity (measured via methacholine bronchoprovocation) was also reported. Dahms et al (31) reported decreases of 21.4 and 20%, respectively, in FEV_1 and FVC in 10 asthmatic patients (5 of whom reported that ETS exacerbated their asthmatic symptoms) when exposed to calculated SS smoke concentrations of 15–20 ppm CO. Stankus et al (129) tested 21 asthmatics who reported that their symptoms were exacerbated by ETS. Fourteen subjects showed no response to SS smoke concentrations as high as 13.3 ppm CO. Of the remaining 7 subjects, 2 showed a decline of at least 20% in FEV_1 with an 8.7 ppm CO exposure and 5 required a concentration of 13.3 ppm CO to exhibit the same response.

Some research into the possible effects of smoke on inflammatory or allergic responses in the nasal cavity has been reported recently. Bascom et al (7) found no evidence for an allergic response to SS smoke concentrations corresponding to 45 ppm CO. Rhinorrhea symptoms and increased nasal resistance were reported in subjects who considered themselves "ETS-sensitive" at this same concentration.

As with the laboratory studies of sensory responses to ETS, the need for research into the possible upper airway effects of ETS at concentrations in the range of those encountered in actual smoking environments is apparent.

Conclusion

Although the scientific literature concerning ETS and its association to human health continues to

grow at a dramatic pace, the difficulty in interpreting the results of these studies leaves many important questions unanswered. Moreover, results from scientific studies conducted to date do not sufficiently support conclusions concerning health effects that might be associated with exposure to ETS. Additional research would prove fruitful in this regard.

Basic questions concerning reliable estimates of ETS exposure, the appropriateness of various biomarkers, the calculation of lifetime dosimetry, the control of confounding factors, the use of meta-analysis, and the relationship between ETS concentrations and human sensory perceptions emphasize the need for additional investigation before conclusions about potential effects of ETS on health or comfort can be made.

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CRITIQUE

Justice, Science, and the "Bad Guys"

When accused of a new offense, does someone regarded as a "bad guy" have the right to due process and a fair trial? If such a right is inherent in the legal systems of civilized society, is it also a part of justice in the "courts" of scientific evaluation? I ask these questions because, in private conversation, I recently heard an authoritative leader in the world of public health epidemiology make the following statement: "Yes, it's rotten science, but it's in a worthy cause. It will help us get rid of cigarettes and become a smoke-free society."

The statement, of course, referred to the data and evaluations assembled in the past few years for accusations about what is formally called *environmental tobacco smoke* and informally designated as *passive smoking*. According to the accusations, this type of exposure causes at least 2 of the prime evils hitherto attributed to direct smoking: lung cancer and cardiovascular disease. In fact, several of the recent cardiovascular studies found risks that were even higher for passive smokers than for direct smokers. (The authors tactfully refrained, however, from stating the implicit conclusion that people who cannot avoid passive exposure should lower their risk by beginning to smoke directly.)

A new part of the current indictment is the claim that passive smoking is responsible for respiratory and otologic difficulties in children. Because young children so rarely engage in direct smoking, pediatricians have hitherto had little participation in the research industry devoted to studying cigarettes. Now, with open hunting season declared on the effects of passive smoking in children, a fertile new opportunity has arisen for selfless public service, fame, grants, and publications.

Nevertheless, if the science is as "rotten" as the public health authority admitted, does the end really justify the means? If objectivity, precautions against bias, and careful operating guidelines are essential for a "bad guy" to get fair treatment in a court of law, should those principles be abandoned or abolished when the "bad guy" is in a court of science?

A peripheral inspection, without any in-depth appraisals, of the current accusations about passive smoking would suggest that many scientific principles have vanished. I shall cite 3 overt examples:

1) Many of the pediatric researchers seem unaware of the frequent disparity between symptoms and objective evidence of ailments whenever people are passively exposed to a "bad guy." Perhaps the most striking demonstration of this phenomenon

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CRITIQUE

Justice, Science, and the "Bad Guys"

When accused of a new offense, does someone regarded as a "bad guy" have the right to due process and a fair trial? If such a right is inherent in the legal systems of civilized society, is it also a part of justice in the "courts" of scientific evaluation? I ask these questions because, in private conversation, I recently heard an authoritative leader in the world of public health epidemiology make the following statement: "Yes, it's rotten science, but it's in a worthy cause. It will help us get rid of cigarettes and become a smoke-free society."

The statement, of course, referred to the data and evaluations assembled in the past few years for accusations about what is formally called *environmental tobacco smoke* and informally designated as *passive smoking*. According to the accusations, this type of exposure causes at least 2 of the prime evils hitherto attributed to direct smoking: lung cancer and cardiovascular disease. In fact, several of the recent cardiovascular studies found risks that were even higher for passive smokers than for direct smokers. (The authors tactfully refrained, however, from stating the implicit conclusion that people who cannot avoid passive exposure should lower their risk by beginning to smoke directly.)

A new part of the current indictment is the claim that passive smoking is responsible for respiratory and otologic difficulties in children. Because young children so rarely engage in direct smoking, pediatricians have hitherto had little participation in the research industry devoted to studying cigarettes. Now, with open hunting season declared on the effects of passive smoking in children, a fertile new opportunity has arisen for selfless public service, fame, grants, and publications.

Nevertheless, if the science is as "rotten" as the public health authority admitted, does the end really justify the means? If objectivity, precautions against bias, and careful operating guidelines are essential for a "bad guy" to get fair treatment in a court of law, should those principles be abandoned or abolished when the "bad guy" is in a court of science?

A peripheral inspection, without any in-depth appraisals, of the current accusations about passive smoking would suggest that many scientific principles have vanished. I shall cite 3 overt examples:

1) Many of the pediatric researchers seem unaware of the frequent disparity between symptoms and objective evidence of ailments whenever people are passively exposed to a "bad guy." Perhaps the most striking demonstration of this phenomenon

occurred in a classic and scientifically superb epidemiologic field investigation on "Subjective Fears and Objective Data." In that landmark study, Spitzer et al (4) showed the excessive frequency with which residents of a Canadian community, exposed to "sour gas" fumes from a nearby mine, complained of diverse ocular, respiratory, neurologic, and other symptoms for which no objective pathology could be found. In an analogous control community elsewhere, where residents were exposed to the same degree of emissions but where their evils had not been publicized, the prevalence of analogous symptoms was substantially lower. Nevertheless, no attention seems to have been given to this phenomenon when symptoms were evaluated for children exposed to the presumptive evil of passive smoking.

2) In meta-analyses of passive smoking studies, as recently pointed out by Fleiss and Gross (2), the investigators have complied with almost none of the scientific guidelines established for this type of research. While agglomerating masses of data obtained *without* randomized trials, the meta-analysts have also given little or no attention to the frequently stated guideline that randomization is a *sine qua non* for the scientific credibility of a meta-analysis.

3) A fundamental rule in criteria for causality is that the evidence from different studies consistently goes in the same direction. This consistency in different investigations of *direct* smoking was one of the key supports in the Surgeon General's Committee's original decision (5) to label cigarettes as a "bad guy." In the investigations of *passive* smoking, however, the various studies are contradictory, some going in positive directions and others not. The inconvenient failure of the evidence to comply with a prime requisite of scientific reasoning for causality, however, has not inhibited the causal accusations. The "prosecution" has simply ignored the inconvenient results and emphasized those that are (in a memorable term) "helpful."

Aside from the problems of getting a fair trial in a court of law, does a "bad guy" also have the right to get a lawyer? If this principle is also a traditional bulwark in systems of justice, what kind of "lawyer" will be available in scientific courts if the act of defending a "bad guy" is almost universally regarded as depraved and immoral? For example, in the current fervor of anti-smoking evangelism, what young scientists would want to risk their careers and what older scientists would want to risk their reputations by doing anything that might be construed as support for the "bad guys" of the tobacco industry? What governmental agency would fund research in which the established "accepted" anti-smoking doctrines were threatened by a study proposed by someone—an obviously deranged skeptic—who wanted to do an unbiased, objective investigation?

The governmental agencies that fund scientific research were once expected to be above the battle, uncommitted, and devoted to seeking truth, however it might be found. For diverse political, social, and fiscal reasons, however, those agencies have often in recent years become mechanisms of advocacy rather than scholarship, pursuing goals of policy rather than science.

Any organization that is under attack—a governmental agency, a foundation, a university, a political group, even a profit-making industry—is always given the right to defend itself by getting a "lawyer," who is usually called a "consultant." This right is apparently also denied to the tobacco "bad guys." Like any other group under attack, the "bad guys" would like to get a respectable, competent consultant—in this instance, an academic or federal investigator of impeccable credentials, who has never been tainted by anything other than federal grants, and who is preferably so disinterested as to believe perhaps that Philip Morris signed the Declaration of Independence and that R.J. Reynolds manufactures aluminum. In the current atmosphere, however, the consultant's stature, credibility, and integrity become instantly impugned and tarnished by the depravity of associating with the tobacco "bad guy."

Another interesting principle is that no one seems troubled when a "good guy" does things that are feared as the behavior of a "bad guy." For example, the National Institutes of Health (NIH) regularly conducts "consensus conferences" in which the main goal is a press release and published document intended to impress Congress into larger allocation of research funds. The assembled participants for these conferences are usually investigators beholden to the NIH for grants (or hopeful of getting them). No one complains that the methods exemplify poor science; the goals and morals are serene, laudable, worthy. No one seems troubled when a federal agency exercises tight censorship over the work of its grantees, as in later years of the Framingham epidemiologic study. Yet large outcries of immorality arise when an investigator doing pure research in basic human biology accepts funds from the Tobacco Industry, given with no strings, no censorship, and complete scientific liberty to pursue the work wherever it leads.

In such an atmosphere, "bad guys" who believe they are getting a "bum rap" will defend themselves as best they can. There thus appears, in this issue of this journal, a review of passive smoking written by four people (3) who have the worst possible background for scientific acceptability. They are not even

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"hired-gun" outside consultants; they are actually directly employed by the tobacco industry.

Many readers will adamantly refuse even to examine a report from such sources. The few who actually begin reading will probably do so with clenched teeth and firm preconceptions. Nevertheless, if science depends on evidence and reasoning, rather than on the sponsoring source, the report is a fascinating document. Expecting a partisan polemic, I found it surprisingly even-handed, well constructed, and well written. It is certainly much better in all these respects than analogous documents prepared by the allegedly disinterested and dispassionate evaluators at governmental agencies. In fact, if the report by Smith et al (3) were published anonymously, with no identification of the authors or their employer, it might well be lauded as an excellent or even model review of the topic.

Instead, however, what the authors have prepared will probably be instantly dismissed because it comes from the "bad guys," and because they failed to do the self-immolation that would have gained approval in the scientific policies of the current status quo. Beyond the authors' sin of engaging in rational self-defense, the editor of this journal will probably be pilloried for publishing the report, and I expect my own share of slings and arrows for failing to castigate it and for even hinting that it may be a worthwhile scientific document.

If public health and epidemiology want to avoid becoming a branch of politics rather than science, the key issues are methods and process (1) not the "goodness" of the goals or investigators. In science even more than law, the "bad guy" (often appearing as a *counter-hypothesis, paradigm shift,* or *skeptical evaluation*) should always have the right to state his case, and a well-stated case has the right to be heard, regardless of who pays for it.

Besides, the "bad guys" sometimes turn out to be correct. Galileo was assailed by the Church when he doubted Earth's centrality in the solar system; Semmelweis was denounced by obstetricians when he said their inadequately cleansed hands were transmitting disease; Florence Nightingale was detested by the British establishment when she campaigned for better sanitation of water and sewage; and Joseph Goldberger was deemed a fanatical nuisance when he questioned an esteemed epidemiologic commission's report that pellagra was an infectious disease.

Just as "bad guys" are sometimes right, the "good guys" are sometimes wrong. The history of medicine and public health is replete with the errors (sometimes harmful blunders) committed by revered, respectable leaders in the field. The most recent memorable public events were the unnecessary, fallacious hysteria about the hazards of Agent Orange, and the needless evacuation of homes (and harm to lives) by residents of an entire town in Missouri, responding to the mistaken zeal of a governmental agency.

The "bad guys," of course, are not always right, but if they are denied a fair and proper scientific hearing, neither society nor science will benefit. Society is entitled to make political decisions based on advocacy. The scientific basis for those decisions, however, should depend not on political advocacy, but on scholarship—no matter how it is produced or by whom.

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DISCUSSION

These calculations have shown that misclassification of smokers as non-smokers, coupled with between-spouse smoking habit concordance, may cause an *apparent* increase in risk of lung cancer among non-smokers married to smokers similar to that observed epidemiologically. Several points arise: (a) the interviews were carried out in a non-emotive, non-health context. In the cotinine study, the subjects were unaware their answers were going to be verified; (b) bias may arise because of misclassification for any reason. In this study, data-handling errors were minimised by careful processing; (c) the increased concordance for heavier smokers may explain the higher observed risk of lung cancer seen in non-smokers married to heavy smokers; (d) in this study, for women, the increase in salivary cotinine associated with spouse smoking was about 0.2% of that associated with active smoking, making a 30% increase in lung cancer risk from passive smoking very unlikely.

It is concluded that most or all of the apparently increased risk of lung cancer in self-reported non-smoking women married to smokers is attributable to bias.

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MISCLASSIFICATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE: ITS POTENTIAL INFLUENCE ON STUDIES OF ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER*

(Passive smoking; response bias)

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SUMMARY

The effects of selection, confounding, misclassification and bias must be eliminated from case-control studies of 'passive smoking' and lung cancer before a meaningful interpretation can be made. Misclassification includes the misclassification of the subject's non-smoking status, of the disease status or of the spouse's smoking habits. This paper shows that inflation of the amount smoked by the husbands of female lung cancer cases may have accounted for the apparent 'dose-response' relationships in 3 widely referenced case-control studies.

INTERPRETATION OF CASE-CONTROL RESULTS

Much of the literature on the association of 'passive smoking' with lung cancer consists of case-control studies of non-smoking women in which exposure to environmental tobacco smoke (ETS) from the husband's smoking is retrospectively estimated by interview of the subject or, if deceased, of a close relative or friend. Apparent 'dose-response' relationships are taken as supporting the claim that exposure to ETS increases the risk of lung cancer, i.e., a causal interpretation. This

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Any views expressed in this paper are those of the author and not of the organization board of the symposium.

Abbreviations: ETS, environmental tobacco smoke.

paper considers the contribution which differential misclassification of exposure might make to these results.

Consider the stages leading to a subject's enrolment in one of these studies. A subject must first be a patient in the selected hospital or hospitals and agree to participate in the study. She must be listed in hospital records or tumor registries as having been diagnosed with the index disease for cases or controls and must satisfy specified demographic criteria with regard to sex, age (possibly) and marital status. In addition, each potential subject must have been listed in hospital records as a non-smoker [1] or be classified as one at interview (note that 40% of women with lung cancer, classified as 'non-smokers' in hospital records, had been smokers at some time or still were, whereas only 8.5% of non-smoking controls were similarly misclassified [1]). Next, the respondent must be selected. This may be the subject herself or her next of kin. The subject's exposure to ETS, usually from her husband, is estimated by interviewing the respondent. The interview may be structured and follow a carefully designed questionnaire or be relatively unstructured.

Each of these stages presents an opportunity for selection bias and misclassification errors to occur. A case-control study of female lung cancer and exposure to ETS therefore presents ample opportunity for artifacts to generate statistically significant results. In addition, confounding may also mimic 'dose-response' effects.

Biased selection of subjects and confounding

Cases, defined as currently married lifelong non-smoking female lung cancer patients, are rare and are not typical of the population. Their 'achieved status' [2] and that of the controls may introduce selection bias into the study. In addition, husband's smoking has been shown to be confounded with age, marital status, education, alcohol and marijuana use [3]. Husbands and wives share the same life style. ETS may therefore be a 'marker' for some other factor.

Misclassification

Misclassification of the subject's diagnosis, her smoking status or of her ETS exposure may occur. Thus, Weiss [4] highlights misclassification of the subject's disease status, her ETS exposure or both as possible explanations for the results found in the epidemiological literature. Misclassification has been shown to attenuate (i.e., underestimate) the true relative risk [5]. By converting to fixed end points, Kraemer [6] has shown that this is true for all measures of association, when misclassification is randomly distributed. Such results assume, however, that the misclassification occurs at the same rate and in the same direction in cases and controls. Misclassification of smoking wives as non-smokers is known to occur [7, 8]. If the wife of a smoker gives up smoking or denies smoking and is consequently misclassified as a non-smoker rather than an ex-smoker or current smoker, her subsequent lung cancer may be associated, in fact, with her smoking rather than

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with her exposure to her husband's smoking. When hospital records are used to classify subjects, substantive misclassification is likely [9]. It has been reported [10] that, since husbands and wives tend to share smoking habits, as little as 5% misclassification among cases can produce a risk ratio of 1.42 in the absence of any effects whatever from exposure to ambient tobacco smoke.

Misclassification may also occur in classifying exposure to husband's smoking, especially if the next of kin responds for a deceased subject (more likely for lung cancer cases than for controls). The respondent is not 'blind', i.e., the respondent knows whether the subject has or had lung cancer or the 'control' disease. In this situation it is postulated that a respondent will tend to inflate the amount smoked by the husband for cases, but not for controls. This is called 'differential misclassification'. As epidemiologists have long recognised, 'when differential misclassification occurs (as in selective recall in case-control studies) the bias can be in either direction and can be great' [11].

METHODS

In the following we estimate the amount of differential misclassification required to mimic the reported results in 3 studies. It is noteworthy that in no study to date has the ETS exposure been measured directly. Rather, a coarse grouping of the amount smoked by the husband is used. This classification is derived from a respondent's answers to questions on the husband's long-term smoking habits, and is, in fact, only weakly associated with the ETS exposure of the non-smoking wife. In fact, 47% of currently non-smoking wives of smokers report less than 1 h per week ETS exposure in the home [3].

The estimation of differential misclassification rates from case-control studies requires an assumption to reduce the number of parameters. We assume that the classification of a case's 'exposure' is biased upwards and that there is no misclassification among controls. Here the husband's smoking habits are categorized so that $i = 0$ represents a non-smoker, $i = 1$ a light, occasional or ex smoker and $i = 2 \ldots m$ increasing amounts of smoking. Now let $P_i p_i$ represent the proportion of cases and controls, respectively, where the husband's smoking level is classified as $i = 0,1$ to m, so that

$$\Sigma P_i = \Sigma p_i = 1$$

Then, if N,n are the number of cases and controls in the study, respectively, a regular 'dose-response' relationship between husband's smoking classification and lung cancer will have proportions $P_i P_j p_i p_j$ such that, for all $i < j$,

$$\frac{P_i}{p_i} < \frac{P_j}{p_j}$$

Because individual cases are at risk of being misclassified, discrete steps of $1/N$ are

taken iteratively to find the minimum misclassification rate which will reproduce the 'dose-response' relationship reported in an individual study. The misclassification rates given below are found by reducing the exposure classification one case at a time until $P_i = p_i$ for all i, to the extent possible with discrete data.

RESULTS

3 case-control studies [1, 12, 13] report statistically significant trends in non-smoking women with lung cancer as the husband's reported smoking classification increases.

Thus, Garfinkel et al. [1] give a progression of odds ratios of 1.00, 1.15, 1.08 and 2.11 for 134 cases and 402 controls reportedly exposed to 0, <10, 10-20 and >20 cigarettes/day smoked by the husband at home. Pooling the intermediate categories gives increasing odds ratios of 1.00, 1.14 and 2.11 for exposures to 0, 1-19 (where 1-19 includes pipe or cigar) and >20 cigarettes/day. Correa et al. [13] give odds ratios of 1.00, 1.18 and 3.52 for reported exposures to 0, 1-40, and >40 pack-years smoked by the husband for 22 cases and for 133 controls. Trichopoulos et al. [12] give odds ratios of 1.00, 1.76 and 2.65 for the 3 exposure categories (non-, former and current smoker) in 40 cases and 149 controls.

Given the assumptions discussed above, Garfinkel's results can arise if 17 of the husbands of his 134 cases are misclassified upwards, a case misclassification rate of 13%. Correa's results can arise if 9 of his 22 cases' husbands are misclassified, a case misclassification rate of 41%. For Trichopoulos, the reported trend could have arisen from a case misclassification rate of 40%, i.e., if 16 of 40 cases' husbands were misclassified upwards. Because of the relatively larger number of cases in the first study [1], the overall case misclassification rate in the three studies required to reproduce the quoted results is 21%.

Although misclassification of exposure among cases has a disproportionate effect on the findings of these studies, another approach is to assume that the rates of misclassification are equal in cases and controls but in different directions. With this assumption, Garfinkel's results [1] can arise from a subject differential misclassification rate of 7%. Likewise, Correa's findings [13] may have arisen from a subject differential misclassification rate of 19%. A 20% overall differential misclassification rate will account for the trends reported by Trichopoulos in Tables 2 and 3 of his paper [12].

DISCUSSION

The findings of 3 case-control studies of lung cancer which show significant trends with 'exposure' to ETS can be generated by postulating differential misclassification of case exposure in the range of 13-40%. The significance of this finding rests on the validity of the underlying assumptions used in deriving these rates of case or subject misclassification.

That misclassification exists in these studies is now widely accepted [3, 4, 9, 14-17]. In general, respondents are more likely to falsely inflate exposure if the case died of cancer than of some other disease [18].

More particularly, there is indirect evidence for the presence and effect of differential misclassification of exposure to ETS. For example, Garfinkel et al. [1] show that the effect of ETS exposure at home is null (an odds ratio of 1) when the case or her husband is the respondent; however, this null result is converted into an odds ratio of 3 when the son or daughter is the respondent.

Again, Table 3 of [15] suggests that differential misclassification may exist. This shows that 4 of 16 spouses of lung cancer cases (25%) contradicted the case by describing themselves as smokers whereas only 1 in 41 (2%) spouses of matched controls contradicted the control by describing themselves as smokers. Here there are two possible explanations. Either the case has denied her husband's smoking, or the husband has exaggerated his own smoking. In practice there is likely to be some behavior of each type. We assume however that this situation is indicative of inflation of the amount smoked by the husband when the case is the respondent.

The most recent case-control study of ETS and lung cancer [15], one which went to some pains to verify exposure classification, provided evidence suggesting a case misclassification rate of exposure as high as 25%. This figure may be compared to the 21% overall case misclassification rate required to produce the results in the 3 studies under review. Both figures may in turn be compared with a misclassification rate of 15% which Letzel and Johnson [19] found was required to invalidate a case-control study of ETS.

In summary, when a spouse's smoking status is used to estimate a non-smoker's ETS exposure, ' a considerable amount of misclassification' [3] may result. Since selection bias and confounding must also be considered, extreme caution is required in the interpretation of these studies. This is especially so when the literature as a whole contains several studies reporting no significant association between ETS exposure and lung cancer [15, 16, 20], as well as various inconsistencies, both among and within studies.

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Lung cancer and passive smoking

SIR,—Your article by Professor Nicholas Wald and others (8 November, p 1217) on passive smoking and lung cancer contained a statistical analysis which was essentially repeated in a report of a committee of the National Research Council of the United States. Professor Wald was a member of that committee and apparently was the principal architect of the epidemiological aspects of that work.[1]

A contemporaneous survey of epidemiological studies on passive smoking and lung cancer was given in an editorial by Blot and Fraumeni in the *Journal of the National Cancer Institute*.[2] The published reports covered by Professor Wald and colleagues and by Blot and Fraumeni largely overlapped. Substantially similar estimates of relative risk were arrived at, 1·34 or 1·35, and in both cases were nominally significant.

Similar concerns about bias were expressed, specifically that women reporting themselves as non-smokers might actually be active smokers or ex-smokers and that non-smoking women not exposed to smoking at home might still have some exposure away from home. Other possibly more serious biases in the studies conducted were not considered. (These include publishing bias: if an investigator got a weakly or insignificantly negative result for the role of passive smoking in lung cancer would he bother submitting it for publication? And if he did, would it be accepted? There seems to be a tendency towards accepting uncritically or less critically manuscripts which are on the right side of the fence on the issue of passive smoking.)

Consideration of the first of these two biases led to a reduction in the estimated relative risk from 1·35 to 1·30 for the paper of Professor Wald and his colleagues but from 1·34 to 1·15 in the National Research Council report. This source of bias cannot fully account for the excess over unity of the relative risk, albeit the National Research Council report suggests that statistical significance would no longer obtain. And the possibility of other biases is noted.

The two survey studies make differing adjustments for exposure to passive smoking away from home. While Professor Wald and his colleagues make an upward adjustment of 18%, from a relative risk of 1·30 to 1·53, the National Research Council report makes an upward adjustment of only 8%, from 1·15 to 1·24.

For assessing statistical significance, this last adjustment is not relevant. It presupposes that passive smoking does increase risk, for if it did not the adjustment would not be needed. But relevance would attach if one wished to estimate the toll in lung cancer attributable to passive smoking.

The National Research Council report notes a study by Jarvis *et al* on biochemical markers of smoke absorption.[3] From that work one would have to judge that the claim of being a non-smoker was more frequently false than has been allowed for in the bias adjustments that have been made. Also, the data on cotinine concentrations in the plasma, saliva, and urine reported by Jarvis *et al* suggest that the relative risk associated with passive smoking would be quite limited, say of the order of 1·05. Passive smokers had, on average, cotinine values 0·5% of the way between the level for those not exposed to passive smoking and the level for active smokers. Assuming active smoking to have a relative risk of 10, added risk of 900%, the predicted relative risk for passive smoking would be 1·045.

It is interesting that the National Research Council report shows a predicted relative risk of 1·14 based on dosimetric considerations. The underlying assumption was that passive smoking had only 1% of the effect of active smoking. That 1% effect was then coupled with a relative risk of 15, added risk of 1400%, for active smoking.

In the event, whether the true relative risk is 1·05 or 1·14, it is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice.

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In conclusion, therefore, the reference bias shown in this study seems to be real. Such a finding has important implications, since there is no reason to believe that rheumatologists are more biased than others in selecting references. A reader tracing the literature on any new drug using the reference lists given in the articles might risk obtaining a biased sample. Reference bias has another serious implication: it may render the conclusion of the individual article less reliable. Is this also true for review articles, and for other disciplines in medicine?

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Towards a reduction in publication bias

ROBERT G NEWCOMBE

Abstract

Current practice results in the publication of many research studies in medical and related disciplines which may be criticised on the grounds of inadequate sample size and statistical power. Small studies continue to be carried out with little more than a blind hope of showing the desired effect. Nevertheless, papers based on such work are submitted for publication, especially if the results turn out to be statistically significant. There is confusion about what makes a result suitable for publication. Often there is a preference for statistically significant results at the peer review stage. Consequently published reports of small studies tend to contain too many false positive results and to exaggerate the true effects.

The use of a criterion of a posteriori power does not eliminate the bias; a priori power is the criterion of choice. This could be implemented by peer review of study protocols at the planning stage by funding bodies and journals.

Introduction

Profound biological and behavioural differences between human beings mean that statistical methods have to be used in presenting medical research findings in an unbiased way. Hence statisticians have devised methods of estimation and significance testing, which are now widely used. Nevertheless, though the mathematical aspects of these methods are acceptable, what is done with the results commonly leads to serious selection bias. An article that reports a statistically significant difference between two treatments is more likely to be published than one which does not. Many research studies have inadequate numbers of subjects, and significance can be attained only if chance conveniently exaggerates the difference.

So long as statistical significance is used as a major criterion of acceptability for publication the published results of medical research will contain a high proportion of false positive results. Thus quantitative estimates of treatment effects taken from published work cannot be regarded as free from bias. There are established methods to calculate the power of a study, which is the probability of detecting a specified, important difference using a test with a set significance level. The interpretation of statistical power is satisfactory only when it is calculated with values specified at the design stage of the study. The proper method to assess the adequacy of the sample size is by peer review of values specified in the protocol. If this is done the significance level eventually attained is no longer relevant to selection for publication.

Importance of sample size

Manuscripts submitted to medical journals often contain serious statistical faults.[1] Various steps have been taken to remedy this,

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notably the checklists used by the *BMJ*,[2] and there is now also an increased awareness of the need for therapeutic efficacy to be evaluated with randomised controlled trials. Nevertheless, power calculations are still rarely used.[3]

Conventional significance testing (table I) leads to great emphasis on the type I error rate α, but the type II error rate β and its complement, the power $1-\beta$, though very important, are neglected.[3] In particular, in a clinical trial the number of subjects required depends on the α and β levels chosen, the treatment difference of interest, and the degree to which the treatment effect varies between subjects. The choice of the first three of these is somewhat arbitrary, and the fourth may be difficult to estimate. Nevertheless, the study is likely to be valid only if values are chosen for these parameters and the resulting sample size requirement determined, whether by the use of formulas,[4] diagrams,[5] or tables.[6]

TABLE I—*The significance testing paradigm. α and β denote the frequencies with which type I errors and type II errors are made. $1-\beta$ is known as the power of the test*

	Decision from significance test	
True state of nature	Accept H_0	Reject H_0
H_0 valid	True negative $1-\alpha$	False positive α
H_0 not valid	False negative β	True positive $1-\beta$

The most obvious consequence of an inadequate sample size is that investigators may well not show a clinically important effect. Such a false negative result, if propagated by publication, is apt to be widely misinterpreted as a demonstration that there is no difference between the treatments. This has provoked two responses among those who decide what is to be published. Firstly, statisticians advocate a shift of emphasis away from significance testing and towards estimation and confidence intervals.[7] A wide confidence interval is understood as implying that large, potentially important differences cannot be ruled out. The confidence interval approach may also help in a wider context—for instance, in showing that the results of two apparently disparate studies are not incompatible, the truth perhaps being somewhere between their two estimates.

The second response is to exclude small studies, with high β, from publication. There are three approaches in which this may be done. Firstly, attainment of a desired level of significance may be used as a criterion. This seems plausible because, for a fixed α, both the attained significance level p and the type II error rate β reflect the sample size. Nevertheless, p (unlike α) depends on sampling variation and the use of this criterion leads to publication bias. Secondly, assessment based on statistical power calculated from the data gives the appearance of greater soundness; it does not fall into the obvious trap of the first approach and is based on data rather than on the uncertainty of a prior targeted difference. In reality, however, the requirement of significance using an α level of 0·05 and an a posteriori β of 0·2 amounts to nothing more than statistical significance at a more stringent level of $\alpha=0{\cdot}005$ and thus also does not avoid publication bias. This kind of β value is akin to p, not to α, and includes sampling variation. The third approach is to impose the requirement of an adequately low β value assessed a priori; this does not lead to bias since the β value is not subject to sampling variation.

Thus results based on studies which had a poor prospect of yielding useful information may justifiably be rejected, but only if the criterion is based on power assessed a priori.

Nature and consequences of publication bias

Publication bias may be defined simply: significant results are preferred for publication. Attention was drawn to it as early as 1963[8] and it has been "rediscovered" several times since. Suppose the α rate chosen is 0·05. Then, just 5% of studies in which H_0 is valid will yield a test statistic significant at the 5% level. If attention is limited to studies that attain publication, however, the proportion of such false positive results is higher. The significance testing paradigm does not permit us to say what proportion of statistically significant results are false positives, but the effect of publication bias is to make this proportion disquietingly larger than it would otherwise be.

Correspondingly, studies selected for publication tend to contain exaggerated estimates of the main effects, and trials with truly modest treatment effects will achieve statistical significance only if random variation conveniently exaggerates these effects.[9] Conversely, variation is underestimated. These biases operate more strongly the more inadequate the sample size. A study with low power, where the true treatment effect is zero or small, must grossly exaggerate it (by chance) to show significance and attain a prospect of publication. False positives and exaggerated estimates may well dominate much of medical publication. This phenomenon is likely to contribute to the disparity commonly found in the results of different studies, which leads to controversy instead of well established, consistent findings. The desire to minimise the impact of false positive assertions may result in a preference for publishing findings which refute a previous claim, rather than confirmatory results—a further source of bias.

Such selection bias may equally be introduced by the editorial team (editorial selection bias) or by the researcher or supervisor or head of department (submission selection bias). At each stage a significant result may be construed as particularly encouraging and failure to attain significance as correspondingly discouraging. This operates in addition to any biases introduced because of prejudice.[10]

Publication bias continues to arise only because two conditions hold: the criteria for selecting studies for publication are inadequate, and many studies performed and submitted for publication have been done on small numbers of subjects. Significance testing, the time honoured framework for inductive inference, is evidently deficient as a selection criterion. Nevertheless, the confidence interval approach incurs the same danger of publication bias: studies in which the confidence interval for the size of the effect excludes zero are likely to be preferred for publication—a condition that is equivalent to statistical significance. It has been asserted that overconcentration on simplistic significance testing is responsible for most of the ill based criticisms of small trials.[11] The more careful approach using confidence intervals overcomes many of the difficulties. But so long as confusion remains as to what constitutes a result warranting publication a bias will ensue from submission and editorial selection processes.

The other prerequisite for publication bias is the widespread use of inadequate sample sizes. The other consequence of this is that a doctor seeking information to guide a clinical decision is confronted with a bewildering variety of conflicting claims. To remedy this dilemma "meta-analyses" or "overviews" have been constructed, which fit together results of several studies and seek to make the best use of data from studies which would otherwise yield little information. Nevertheless, published studies are still a biased sample of all the relevant work that has been done. The only prospect of eliminating this bias is to contact all investigators who may have done relevant work and ask for their unpublished data. Iain Chalmers and Thomas Chalmers are pursuing this goal in connection with the Oxford Database of Perinatal Trials, and their work should provide some evidence on the quantity of "negative" studies that either never get written up or never get published.

The high prevalence of small studies stems from the way that research is organised. Much material submitted for publication has come from studies that are regarded as the work of an individual researcher, performed within severe constraints of time and resources; often there is little more than a blind hope that the desired effect will be shown. Research output remains a major criterion for assessing candidates for promotion and so on, even though it is widely recognised to be deficient. When research output is equated with publication, however, the consequences for the standards of published work are grave. The constraints an individual investigator faces often preclude obtaining results of

external validity, but publication in a highly regarded, widely circulated journal implies such validity, however mistaken this is given the background of inadequate statistical power.

Thus the researcher faces a dilemma: on the one hand, most studies he can perform will need the collaboration of others to attain adequate statistical power; on the other hand, any collaborative study (even if it is feasible) will deprive him of personal kudos. Only those who are remote from the researcher's dilemma—journal editors and referees, funding bodies, and (to a lesser degree) ethical committees—can uphold the highest scientific standards with no conflict of loyalties. These agents are not obliged to accept the status quo and can refuse to support or publish inadequate research. I regard it as their prerogative, if not obligation, to do so.

A radical proposal

Selection of work for funding or publication, then, should primarily be based on reasonableness a priori: Has the design adopted (explicitly or implicitly) a good prospect of yielding useful information? "Design" here includes the study idea, scientific basis, clinical relevance, originality, and so on, as well as the study's structure and the number of subjects. If all this is satisfied then the paper should be published irrespective of whether statistical significance or the targeted size of difference was attained. The difference actually observed is irrelevant to the decision (see Mahoney,[10] p 163). The assessment of scientific validity would therefore be the same, whether carried out before the study or after it. The only additional requirement a posteriori is adequate adherence to the protocol—in particular, attainment of the planned sample size.

The consequences of this shift in emphasis to a priori criteria are most important in the case of studies of inadequate power. Table II contrasts what would happen to the results of these studies under the proposed rule with what is likely to happen at present. The publication of "positive" findings would be inhibited. The advantage would be the exclusion of false positives from inadequate studies, with their grossly exaggerated estimates of differences. Against this must be weighed the cost of failing to publish true positives—which would occur quite often ($1-\beta=0\cdot5$), but which are based on inadequate evidence and also overestimate the difference.

Application of this principle to studies with adequate power would lead to more widespread publication of negative results (table III). True negative results would be salvaged from studies of acceptable power—though these might currently be accepted anyway, especially if supplemented with confidence intervals. This would be at the cost of publishing studies with false negative results, though these would not be too frequent ($\beta=0\cdot1$).

TABLE II—*Consequences of a shift to assessment by a priori power. The case of a study with inadequate power: $1-\beta=0\cdot5$, $\alpha=0\cdot05$*

	Decision from significance test	
	Accept H_o	Reject H_o
Whether published under:		
Present practice	?No	Yes
Proposed policy	No	No

Both journal editors and funding bodies can and should require specification of statistical power. They should require that a protocol or a write up should describe clearly the details of the design of the study—in particular, the following:

(*a*) the structure;

(*b*) the choice of the most appropriate criterion variable on which to base the power calculation and the most appropriate groups to be compared;

(*c*) the size of the effect to be reliably detected and (except in the case of a binary variable) how much this effect varies between subjects;

(*d*) the sample size (specifying accrual rate and period) aimed at, with specific allowance for expected dropouts;

(*e*) consequent statistical power and the method by which it was derived.

These parameters should be identical in the protocol and in the eventual study report. The same criterion should be used to assess validity at both stages—in particular, the write up should be assessed on the basis of the values laid down before any data were collected. The only additional requirements at the publication stage would be the completion of the study as laid down in the protocol, with full information on as many subjects as were contracted for; variability in response between subjects not grossly in excess of that planned for; and the usual standards of adequate analysis, inference, and discussion.

TABLE III—*Consequences of a shift to assessment by a priori power. The case of a study with adequate power: $1-\beta=0\cdot9$, $\alpha=0\cdot05$*

	Decision from significance test	
	Accept H_o	Reject H_o
Whether published under:		
Present practice	?No	Yes
Proposed policy	Yes	Yes

This approach entails assessment of the parameters assumed on an a priori basis; they are to be judged in the light of knowledge current at the time the study was designed. Other results coming to light during the study should not be allowed to affect the judgment of validity (though occasionally a major advance occurring during this period may render the results no longer relevant).

Journal editors as well as grant awarding bodies could implement this proposal most effectively by requiring submission of protocols for peer review at the planning stage. In either case an independent review body could be used. Specialists in the subject could assess the reasonableness of the values supplied for the parameters on which the power calculation is based (particularly the smallest clinically important difference), and the verification of the power calculation would not be a formidable task for a statistician or other assessor familiar with this. These assessments, once performed for the protocol, would not need to be repeated for the write up. Consequently, having accepted a protocol as adequate and relevant, a journal could offer eventual publication, conditional only on completion of the study in adequate conformity to the protocol together with the usual requirements of adequate analysis, inference, and discussion. It would become normal practice to accept an article only if this had been done.

The work of Mahoney suggests that reviewers may find it difficult to comment on incomplete manuscripts.[10] Nevertheless, Mahoney's study is not an ideal model for the process I advocate, for two reasons. Firstly, his reason for the incompleteness of the manuscript was inadequate. It would be understood, however, that the material to be evaluated was only a protocol, even though it would be virtually unaltered in the eventual article—and this would become an accepted element of peer review (as it is, to a limited extent, with funding bodies). Secondly, Mahoney studied psychologists known to have entrenched, diametrically opposite beliefs, to a degree (I hope) not encountered often among doctors; knowing that results would shortly be disclosed, they would be reluctant to commit themselves unequivocally to a favourable stance, lest the results turned out to contradict their chosen position. At the stage of review of a protocol this possibility is more remote.

To put these recommendations into practice would be more feasible for formal, well structured study designs, such as the clinical trial, than for less formal explanatory work—for which the rationale of significance testing is more contentious. Like other alterations in editorial policy, this would best be introduced as a decisive change, as from a given date, with advance indication given, as a piecemeal approach to change is unlikely to work.[11] I

hope that enlightened editors will take up the challenge; the lead must come from an established, prestigious journal that can afford to be choosy.

Conclusion

Publication bias is endemic and will remain so as long as the sample sizes commonly used in research are too small and the methods used to assess adequacy of sample size are deficient. Assessment by a priori criteria—in particular, systematic peer review at the planning stage—would result in a much tighter measure of control over the quality of published work, with the prospect of improvement in study design in general and statistical power in particular.

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Medicine and the Media

AT THE ANNUAL scientific meeting of the British Paediatric Association last year the prize for the best paper presented by a young paediatrician went to a member of a research group from Oxford. Papers offered for the annual meeting are examined by the association's academic board not only for their scientific worth but also for adherence to ethical standards. This paper, later published in the *Lancet*,[1] has now been condemned by certain sections of the press and by a group of members of parliament. What was the work so condemned?

Preterm infants of low birth weight live at considerable risk, particularly of cardiorespiratory failure, and the risk is increased if they have to undergo an operation. Clinical experience suggested that deep anaesthesia and narcotic analgesics would increase the risk. That and the belief that such infants have a poor perception of pain because of lack of myelinisation in the central nervous system led to the conventional practice of anaesthesia with nitrous oxide and muscle relaxants combined with artificial ventilation. In a study of 40 published reports the Oxford team found that three quarters of newborn babies undergoing surgical ligation of patent ductus arteriosus had received muscle relaxants alone or with nitrous oxide.

In the preterm infant with a poor or absent ability to cry it is difficult to tell clinically whether pain and stress are being experienced, but newer biochemical methods that detect hormones and intermediary metabolites associated with stress now make the assessment of stress more possible and prompted a re-examination of the problem by the Oxford team. The team wanted to find out whether adding a little narcotic analgesic to the accepted anaesthetic regimen might prove beneficial rather than harmful. Using these metabolic methods, they therefore compared the response to surgical ligation of patent ductus arteriosus carried out under the conventional regimen with and without the narcotic analgesic fentanyl. The possibility that fentanyl might adversely affect respiration and circulation postoperatively was also studied.

A randomised trial was designed with help from the National Perinatal Epidemiology Unit in Oxford to ensure that the results were statistically valid and that a meaningful result would be recognised as soon as possible. After only eight babies in each group had been operated on the results showed that the new regimen was significantly superior to the old not only in reducing the stress response estimated biochemically but also in improving the postoperative state. Thus for the first time good scientific evidence was produced of the need to provide deeper anaesthesia during operations on these tiny infants.

This research was commended by the distinguished American paediatrician Dr William Silverman, author of the widely acclaimed book *Human Experimentation: A Guided Step Into the Unknown*.[2] He wrote that the Oxford workers "deserve a loud vote of thanks for the ethically sound effort to subject to a rigorous test opinion based on long standing practice. And their call for further study should not fall on deaf ears. It is indeed urgent to determine the pathophysiological consequences of unrelieved pain and suffering inflicted during everyday care of newborn babies."

Members of the British Paediatric Association were thus amazed and the doctors who had done the work bewildered and distressed when after a distorted report in the *Daily Mail* entitled, "Pain-killer shock in babies' operations" (8 July) this work became the subject of a condemnatory "press release: for immediate publication" issued by some members of parliament forming the All Party Parliamentary Pro-Life Group. The *Lancet* article appeared in January, the story in the *Daily Mail* in July, and the press release from the members of parliament in August. The press release was entitled "Inhumane baby operations slammed" and the first paragraph stated:

"Fourteen members of parliament have demanded an inquiry into trials in which sixteen premature babies were given open heart surgery, eight of them without the use of pain killers to test whether or not the babies could experience pain."

The press release then said that the General Medical Council was being asked to investigate these trials with a view to bringing those responsible before its disciplinary committee. It continued:

"In a statement Sir Bernard Braine said:

'The trials seemed to us to be even more barbarous when one considers that the babies being tested for pain were given curare, a paralysing drug, so that they would have been unable to kick or struggle even if they were in agony, the obvious intention being to keep them immobile at all costs throughout the operation. Apart from this they were given only nitrous oxide (laughing gas).'"

Implying misleadingly that wisdom acquired from the research existed before it was carried out the statement went on:

"Not surprisingly post-operatively they fared far worse than the eight babies who were given pain killers. Two of the disadvantaged babies suffered from hypotension, two showed poor peripheral circulation—both of which can be indications of shock which most

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QUESTIONNAIRE ASSESSMENT OF LIFETIME AND RECENT EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

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Coultas, D. B. (New Mexico Tumor Registry, Cancer Center, U. of New Mexico Medical Center, Albuquerque, NM 87131), G. T. Peake, and J. M. Samet. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am J Epidemiol* 1989;130:338–47.

In a sample of 149 adult nonsmokers recruited in New Mexico in 1986, the authors assessed the reliability of questionnaire responses on lifetime exposure to tobacco smoke in the home. They also compared urinary cotinine levels with questionnaire reports of environmental tobacco smoke exposure during the previous 24 hours. The agreement of responses obtained on two occasions within six months was high for parental smoking during childhood: 94% for the mother and 93% for the father. For the amounts smoked by the mother and the father during the subject's childhood, the agreement between the two interviews was moderate: 52% and 39%, respectively. For the number of hours per day that each parent smoked in the home during the subject's childhood, the Spearman correlation coefficients also indicated only moderate reliability ($r = 0.18$ for maternal smoking and $r = 0.54$ for paternal smoking). For each set of interviews, responses concerning recent tobacco smoke exposure and urinary cotinine levels were correlated to only a modest degree. The authors conclude that adults can reliably report whether household members smoked during their childhood, but information on quantitative aspects of smoking is reported less reliably.

pyrrolidinones; questionnaires; tobacco smoke pollution

The term "passive smoking" refers to the involuntary exposure of nonsmokers to the combination of tobacco combustion products released by the burning cigarette and smoke components exhaled by the active smoker (1, 2). The adverse health effects of passive smoking on children and adults have been described in numerous epidemiologic investigations (1, 2). However, despite the evidence linking malignant and nonmalignant diseases with active and passive smoking, tobacco smoking remains highly prevalent worldwide (1). In the United States at present, about 30 per cent of adults are active cigarette smokers (3), so that a large proportion of nonsmokers

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in this country are involuntarily exposed to environmental tobacco smoke (1, 2).

Although some health effects of passive smoking have been convincingly demonstrated, many questions on the health effects of passive smoking remain unanswered. More precise description of exposure-response relations is needed for assessment of the adverse effects on children and the development of lung cancer. Additionally, further studies on exposure to environmental tobacco smoke in the workplace are warranted because of the high prevalence of smoking among adults and public concern about this source of exposure. In most epidemiologic studies on involuntary smoking published to date, exposure has been assessed with questionnaires; for the purposes of some investigations, the questionnaires have spanned the entire lifespans of the subjects. Questionnaires will remain the most feasible method for assessing exposure to environmental tobacco smoke in new studies. However, the reliability and validity of questionnaire measures of involuntary smoking have not been adequately characterized.

In this study, we have assessed the reliability of a comprehensive questionnaire on lifetime exposure to environmental tobacco smoke in 149 adult nonsmokers. While validity is also of interest, no appropriate standard for comparison is available for a lifetime history. Questionnaire responses with poor reliability are also likely to have poor validity. In this sample, we also examined the relation between reports of recent exposure to environmental tobacco smoke and urinary cotinine levels.

MATERIALS AND METHODS

Sample selection

Between February and December of 1986, nonsmokers aged 18 years and older were recruited from Albuquerque, New Mexico, and the surrounding communities. Recruitment was accomplished by two methods: advertisements and direct contact with subjects from a population survey (4). In both approaches, we asked for volunteers to participate in a study of indoor air quality that involved completing a questionnaire on two occasions and providing saliva and urine samples. The subjects were not informed that the study was directed specifically at exposure to environmental tobacco smoke. We attempted to stratify the sample uniformly by age and by sex but were not completely successful (table 1). Of our sample, 62 per cent were female, and only five males were aged 60 years and older.

Data collection

A structured questionnaire on lifetime and recent exposure to environmental tobacco smoke was administered by a trained interviewer to each subject on two occasions separated by approximately four to six months. Training involved familiarization and practice with the questionnaire and review of probing techniques, which were standardized. The interviews were conducted by four interviewers who completed 89.2, 5.4, 2.7, and 2.7 per cent of the first interviews and 38.2, 6.7, 54.4, and 0.7 per cent of the second interviews, respectively. We asked whether the subject's mother had smoked while pregnant with the subject, and we determined the smoking status of parents, spouses, and others from questions on whether these persons had smoked in the subject's home on a daily basis for six months or more. These questions referred to two time periods: birth to age 18 years and age 19 years to the time of the interview. These time periods were chosen to correspond to the usual ages for

TABLE 1
Age and sex distribution of 149 participants in a study of involuntary exposure to tobacco smoke, New Mexico, 1986

Age (years)	Males		Females	
	No.	%	No.	%
20–29	12	21.4	17	18.3
30–39	20	35.7	27	29.0
40–49	9	16.1	15	16.1
50–59	10	17.9	15	16.1
≥60	5	8.9	19	20.4

living in the parents' home and subsequently living outside the parents' home. In addition, for each smoker, we asked about the type(s) of tobacco smoked (cigarette, pipe, or cigar), the amount of each type smoked in the home, the number of years each type was smoked, and the number of hours of exposure per day to each type in the home. Another set of questions asked about the amount of exposure during the previous 24 hours. The questions covered the number of smokers to which the subject was exposed, the type(s) of tobacco smoked (cigarette, pipe, or cigar), and the number of hours of exposure. These questions were asked separately for exposures at home, at work, in vehicles, and at social gatherings. At the time of the interview, a urine specimen was collected and frozen at −20 C until the cotinine assays were performed.

Cotinine assay

Cotinine was quantitated by a double antibody radioimmunoassay as described by Langone et al. (5). A specific antiserum produced in rabbits was supplied by Dr. Helen Van Vunakis of Brandeis University (Waltham, MA). Urine samples were diluted 1:4 for the assay. The sensitivity of the assay in our hands was 36 pg/tube or 0.78 ng/ml of urine (4,204 pmol/liter). Urinary creatinine concentrations were determined by the Jaffe reaction (6), and the cotinine concentrations were standardized to the creatinine concentrations. Assays were performed without knowledge of questionnaire responses.

Data analysis

Reliability was assessed by comparison of the two lifetime histories for the exposure variables during the two time periods, birth to age 18 years and age 19 years to the time of the interview. Because of the small number of pipe and cigar smokers among parents ($n = 24$) and spouses ($n = 4$), we restricted our analysis to cigarette smokers. We summarized the per cent agreement between the first and second interviews for categorical variables, which included mother's smoking during pregnancy; mother's, father's, and spouse's cigarette smoking status; amount smoked, categorized as less than one pack per day, one pack per day, and more than one pack per day; and number of other cigarette smokers in the household, categorized as none, one, and two or more. To discount chance agreements between the first and second interviews, Cohen's kappa was calculated for all categorical items and tested for significance (7, 8). Spearman rank order correlation coefficients (9) were calculated for continuous variables, which included both the number of years and the number of hours per day that the subject's mother, father, spouse, and others had smoked.

For questions on exposure to tobacco smoke during the previous 24 hours, we created summary variables for cigarette smoke exposure only, because exposure to pipe and cigar smokers was infrequent. The summary variables for cigarette smoke exposure included the total number of hours of exposure and the total number of cigarette smokers in all locations. To examine the relation between measures of short term exposure to environmental tobacco smoke within and between interviews, we calculated Spearman rank order correlations (9).

Data analyses were performed with standard programs of the Statistical Analysis System (10).

RESULTS

Of the 158 subjects enrolled for the first interview, 149 (94 per cent) also completed the second interview. Of the nine subjects who were not reinterviewed, there were seven males and two females, with mean ages of 43.6 years and 43.0 years, respectively. This report is based on responses of those 149 subjects who were reinterviewed. The age range of the 149 subjects was 21–79 years (mean = 43 years); 37.6 per cent were males and 62.4 per cent were females (table 1). The median duration between

interviews was 17 weeks, with a range of 6–35 weeks.

For the period birth to age 18 years, agreement between the first and second interviews was high for parental smoking status during childhood (table 2). The per cent agreement was similar for mother's and father's smoking during childhood and was lowest for maternal smoking during pregnancy. The percentage of unknown responses was highest for maternal smoking during pregnancy. The per cent agreement and kappa statistic for the number of other cigarette smokers in the home during childhood were 77.0 per cent and 0.47 ($p < 0.0001$), respectively.

In contrast to the high reliability of responses about parental smoking status during childhood, concordance was low for responses about the usual amount smoked in the home by the parents during childhood (table 3). The concordance was highest for the amount smoked by the mother and lowest for the amount smoked by the fa-

TABLE 2

Percentage of nonsmokers reporting exposure to parental cigarette smoking during childhood, New Mexico, 1986

Response	Maternal smoking during pregnancy (n = 149)	Maternal smoking during childhood (n = 149)	Paternal smoking during childhood (n = 149)
Yes			
First interview	20.1	36.9	55.7
Second interview	20.1	32.9	56.4
No			
First interview	67.1	62.4	43.6
Second interview	64.4	67.1	42.9
Unknown			
First interview	12.8	0.7	0.7
Second interview	15.5	0.0	0.7
Agreement			
Concordance	85.9	94.0	92.6
Kappa	0.73*	0.87*	0.85*

* $p < 0.0001$.

TABLE 3

Percentage of nonsmokers reporting exposure to various amounts of cigarettes smoked by the parents during childhood and by the spouse during adulthood, New Mexico, 1986

Amount smoked	Maternal smoking during childhood (n = 48)	Paternal smoking during childhood (n = 79)	Spousal smoking during adulthood (n = 64)
Less than one pack/day			
First interview	62.5	70.9	84.4
Second interview	50.0	35.4	40.6
One pack/day			
First interview	20.8	11.4	7.8
Second interview	22.9	32.9	31.3
More than one pack/day			
First interview	6.3	10.1	6.3
Second interview	16.7	22.8	28.1
Unknown			
First interview	10.4	7.6	1.6
Second interview	10.4	8.9	0.0
Agreement			
Concordance	52.1	39.3	43.8
Kappa	0.22*	0.04*	−0.04*

* $p > 0.05$.

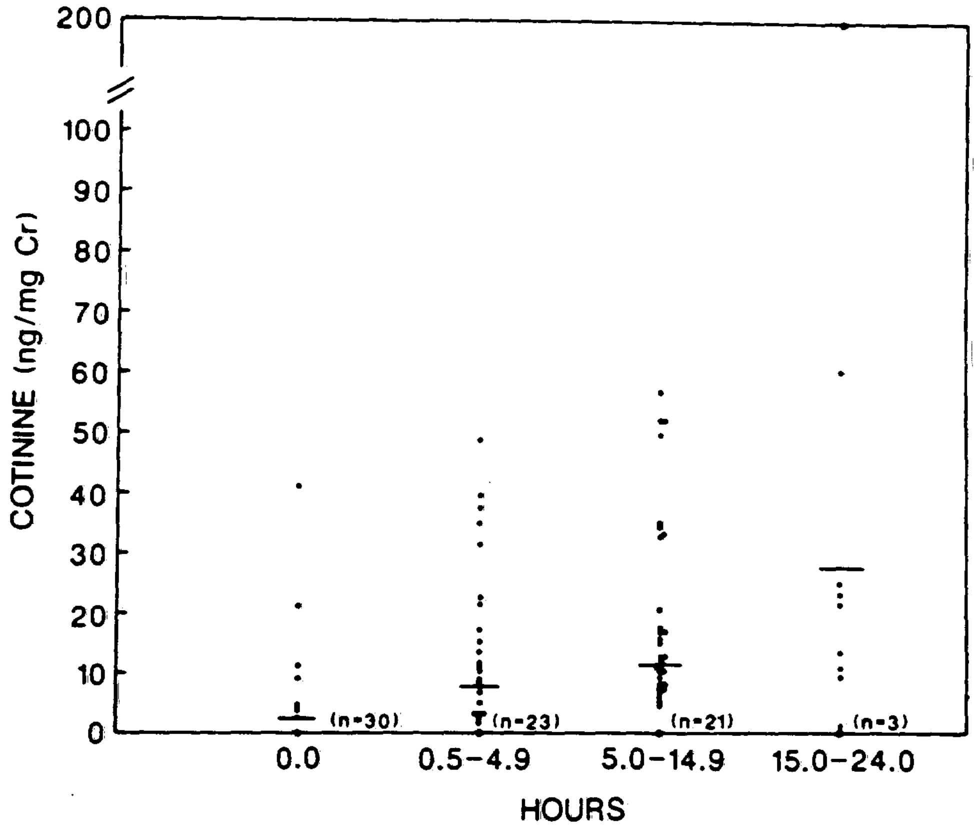

FIGURE 2. Urinary cotinine levels, standardized to urinary creatinine (Cr) concentration, among nonsmokers interviewed about tobacco smoke exposure, by the self-reported total number of hours that the subject was exposed to cigarette smoke during the 24 hours prior to the first interview. Bars show the mean cotinine level for each group. Values in parentheses indicate the number of subjects with nondetectable levels of cotinine. New Mexico, 1986.

and second interviews, the mean responses for the reported number of cigarette smokers that the subjects had been exposed to during the previous 24 hours were 2.1 and 1.8, respectively, with 20 subjects at the first interview and 22 subjects at the second interview reporting exposures in "crowds." For the total number of hours of exposure during the previous 24 hours, the mean responses at the first and second interviews were 5.1 and 4.6, respectively. Both the questionnaire variables and the cotinine data indicated a relatively stable pattern of exposure. The Spearman correlation coefficients were somewhat higher for the questionnaire-based indexes than for urinary cotinine levels.

DISCUSSION

In a group of adult nonsmokers, we found high reliability for reports on parental smoking and on smoking by others in the home (table 2) but lower reliability for semiquantitative exposure measures (tables 3–5). Mean levels of urinary cotinine increased with exposure to cigarette smoke compared with no exposure ($n = 37$) (figures 1 and 2). However, within specific levels of exposure, the cotinine levels varied widely. Across the follow-up period of sev-

TABLE 6

Spearman correlations between measures of exposure to environmental tobacco smoke during the 24 hours prior to interview, New Mexico, 1986

Exposure variable	No.	r
Total no. of smokers to which subject was exposed		
Responses at the first and second interviews	143	0.50
Response at the first interview and cotinine level	143	0.24
Response at the second interview and continine level	139	0.21
Total no. of hours that subject was exposed to cigarette smoke		
Responses at the first and second interviews	144	0.62
Response at the first interview and cotinine level	145	0.32
Response at the second interview and cotinine level	138	0.29
Cotinine level		
Levels at the first and second interviews	140	0.45

eral months, exposures to environmental tobacco smoke were relatively stable, as were urinary cotinine levels (table 6). Most subjects were able to provide responses to the questions on maternal smoking during pregnancy, parental smoking during childhood, and smoking by a spouse during adulthood (tables 2 and 3).

Several limitations of these data must be considered. Because a standard for validating a lifetime history of exposure to environmental tobacco smoke is unavailable, we used repeatability as an index of the quality of questionnaire responses. We addressed the reliability of questions on lifetime exposure at home, but not in the workplace, an important source of exposure for a substantial proportion of adults (11). Interview with a volunteer subject does not replicate the usual setting of a case-control study, the design most often used to examine lung cancer and passive smoking (1). In that setting, recall bias by ill subjects may affect reliability of questionnaire responses in comparison with a volunteer population.

Similar observations on the reliability of questionnaire data on passive smoking were recently reported by Pron et al. (12). These investigators interviewed 117 subjects, controls in a case-control study of lung cancer, on two occasions separated by an average of six months. Smoking by spouses was reported with high reliability (kappa = 0.89 for both wife and husband). Repeatability was somewhat lower for smoking by the mother (kappa = 0.76) and by the father (kappa = 0.44). As in the present study, repeatability of quantitative estimates of duration of exposure was lower than for the categorical descriptions of smoking by household members.

Although neither the investigation of Pron et al. (12) nor the present study directly addresses validity of questionnaires on lifetime passive smoking, the validity of subjects' reports on smoking by parents and spouses has been described. Sandler and Shore (13) compared responses on parents' smoking given by cases and controls with responses given by the parents or siblings of the index cases. Concordance was high for whether the parents had ever smoked, although the agreement was somewhat better for smoking by the mother than for smoking by the father. Responses concerning numbers of cigarettes smoked did not agree as highly. In a follow-up study of a nationwide sample, children's responses on smoking by their deceased parents closely agreed with the information given 10 years previously by the parents themselves (14). Other studies have shown that people generally report the smoking habits of their spouses correctly (14–19). However, people's reporting of quantitative aspects of the smoking behavior of their spouses tends to be less valid (16, 18, 19).

Smoking by parents during childhood and by a spouse during adulthood represent the most important sources of household exposure to environmental tobacco smoke. The studies of subject reports for parents and spouses indicate good validity of responses on smoking by these household

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members; the study of Pron et al. (12) and the present study show that these reports are also highly reliable. Thus, exposure measures based on cigarette smoking status of parents and of spouses, as reported by an index subject, are reported with a high degree of validity and reliability, although these measures may only crudely quantitate the dose of biologically relevant tobacco smoke components. In contrast, the accuracy of more quantitative measures of smoking by these household members is lower. The resulting misclassification may explain the failure to find exposure-response relations for passive smoking and lung cancer in some studies (1, 20).

We also compared responses to questions on exposure during the previous 24 hours with urinary cotinine level. The time period for the questionnaire was limited to the previous 24 hours to reduce bias from faulty recall. However, since this period is approximately the half-life of cotinine in nonsmokers (21, 22), the cotinine level represents not only exposure during the 24 hours covered by the questionnaire but prior exposure as well.

We found modest correlations between the questionnaire-based measures of exposure and urinary cotinine levels (table 6). The level of correlation must be interpreted in the context of the different lengths of time of exposure assessed by the questionnaire and by the urinary cotinine level. Furthermore, at a given level of nicotine exposure, urinary cotinine level is also influenced by uptake, metabolism, and excretion, which are likely to vary among individuals.

Coultas et al. (23) found that questionnaire measures of household exposure were not strong predictors of salivary cotinine level. In 247 adult nonsmokers with a detectable cotinine level, the subject's age, the number of cigarettes smoked per day by the spouse, and the number of cigarettes smoked per day by other smokers in the household explained only 2 per cent of the variance in cotinine levels for females and 16 per cent of the variance for males. Even in active smokers, questionnaire responses on smoking behavior do not tightly predict cotinine concentrations in body fluids (24–27). Higher correlations between urinary cotinine levels and reported exposure to cigarette smoke have been reported for young children (28). The higher correlations in the studies of young children probably reflect the time-activity patterns in this age group (29); parental smoking in the household is generally the dominant source of exposure.

In adults, the weak relation between cotinine level and reported smoke exposure implies that a single cotinine measurement should not be used to estimate exposure for individuals (23). However, in our subjects, cotinine levels varied among exposure groups (figures 1 and 2), suggesting that cotinine measurements might be used as an index of mean exposure for members of a particular exposure group.

Nonsmokers are exposed to environmental tobacco smoke in many different environments, including the home, the workplace, and other private and public locations. Since subjects in an epidemiologic investigation cannot be expected to comprehensively describe the extent of exposure in each of these environments, misclassification of the amount of exposure to environmental tobacco smoke must be anticipated from the use of questionnaires. However, subjects can provide valid and reliable reports concerning the smoking status of household members. The combination of questionnaires and biologic markers offers a feasible approach for assessing recent exposure to environmental tobacco smoke.

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ther. Compared with the first interview, the percentage of subjects reporting parental smoking of one pack per day or more was higher at the second interview.

We also examined the reliability of responses on smoking status and amount smoked by sex and by age. The findings were similar to the overall analysis within strata defined by either sex or age, above and below age 40 years.

Spearman correlations were used to describe the agreement between the first and second interviews on the reported number of years and hours per day of exposure to environmental tobacco smoke during childhood. The correlation coefficients were high for responses on the number of years the parents and other smokers in the household had smoked (table 4). However, for responses on the number of hours per day of smoke exposure in the home, the correlation coefficients were much lower (table 4).

We next examined the reliability of reported smoke exposure during adulthood (tables 3 and 5). After age 18 years, the numbers of subjects living with either their mother ($n = 8$) or their father ($n = 9$) were small. For this small group of subjects, the concordance of responses on parental smoking status was 100 per cent. Similarly, the per cent agreement on spouse's smoking status, as obtained at the two interviews, was 100 per cent ($n = 67$). For the amount currently smoked by the spouse, the concordance was lower (table 3). Agreement between responses about the number of other cigarette smokers in the household

TABLE 4

Mean years and hours per day of childhood cigarette smoke exposure reported by nonsmokers, New Mexico, 1986

Exposure variable	No.	First interview	Second interview	Spearman's r
Maternal smoking				
Years*	33	15.4	15.7	0.76
Hours/day†	31	5.0	6.4	0.18
Paternal smoking				
Years	57	16.1	15.4	0.75
Hours/day	56	4.8	4.8	0.54
Other household members' smoking				
Years	28	13.9	13.2	0.63
Hours/day	20	9.2	8.4	0.51

* "During the period from birth to age 18 years, for how many years did he/she smoke cigarettes?"

† "On average, during the period from birth to age 18 years, for how many hours per day were you exposed to individuals' cigarette smoke?"

TABLE 5

Mean years and hours per day of adulthood cigarette smoke exposure reported by nonsmokers, New Mexico, 1986

Exposure variable	No.	First interview	Second interview	Spearman's r
Spouse's smoking				
Years*	40	16.2	16.4	0.96
Hours/day†	39	5.9	5.5	0.25
Other household members' smoking				
Years	67	8.3	8.2	0.78
Hours/day	58	12.7	10.3	0.54

* "For how many years did he/she smoke cigarettes while you were sharing your home?"

† "On average, how many hours per day were you exposed to their cigarette smoke?"

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was 74.0 per cent ($n = 66$), with a kappa value of 0.50 ($p < 0.0001$).

Correlations between responses at the two interviews were high for the number of years the spouse and other smokers in the household had smoked during the subject's adulthood, but much lower for the number of hours per day of exposure during adulthood (table 5). Because of the small number of subjects living with their parents after age 18 years, we did not calculate correlation coefficients for these variables.

Urine specimens were obtained from 98 per cent of the 149 subjects at the first interview and 95 per cent at the second interview. The median urinary cotinine levels were zero at both interviews, with mean levels of 9.2 ng/mg of creatinine at the first interview and 7.3 ng/mg of creatinine at the second interview. Cotinine levels varied widely with the total number of smokers and the total number of hours of exposure to tobacco smoke (in various situations) during the 24 hours prior to urine collection at both the first interview (figures 1 and 2) and the second interview (data not shown). The cotinine levels correlated only modestly with the questionnaire measures of exposure (table 6).

We also assessed the stability of data on exposure, as measured by questionnaire and by cotinine level (table 6). At the first

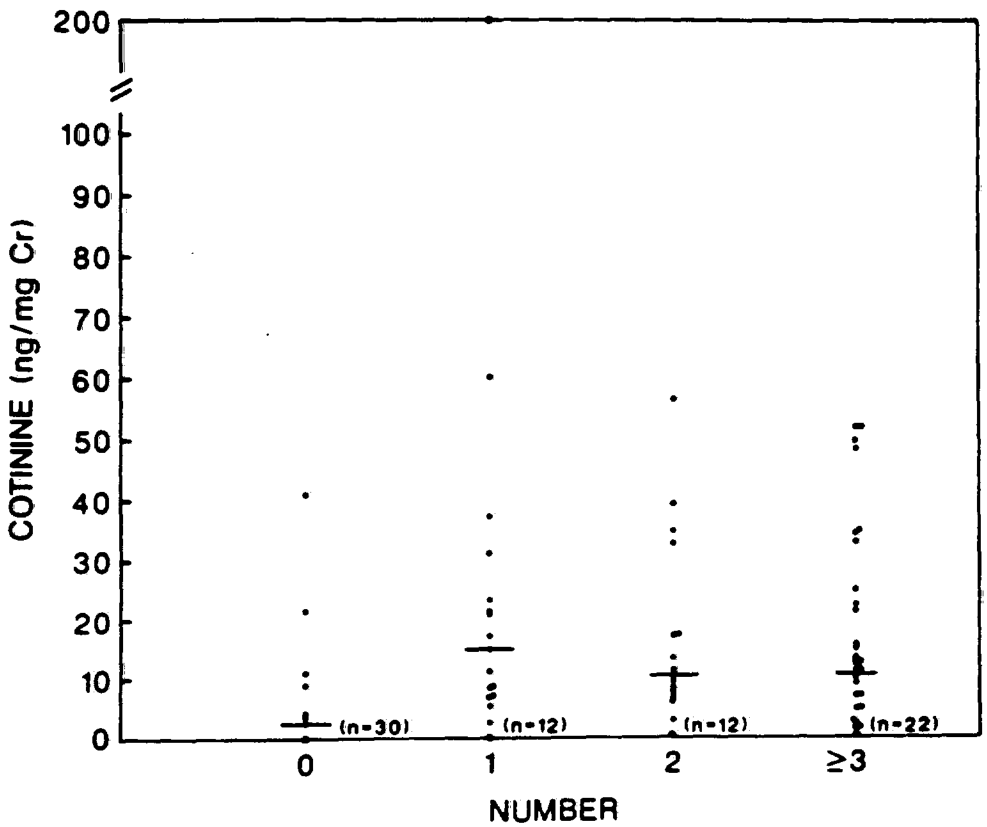

FIGURE 1. Urinary cotinine levels, standardized to urinary creatinine (Cr) concentration, among nonsmokers interviewed about tobacco smoke exposure, by the total number of cigarette smokers the subject reported being exposed to during the 24 hours prior to the first interview. Bars show the mean cotinine level for each group. Values in parentheses indicate the number of subjects with nondetectable levels of cotinine. New Mexico, 1986.

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A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke

David B. Coultas, MD, Jonathan M. Samet, MD, John F. McCarthy, ScD, and John D. Spengler, PhD

Abstract: We enrolled 15 nonsmoking volunteers to evaluate the feasibility of measuring personal exposure to environmental tobacco smoke (ETS) at work and to characterize workplace exposures. During one workshift, we obtained questionnaires on exposure, saliva and urine for cotinine, and personal air samples for respirable particles and nicotine. The levels of cotinine, respirable particles, and nicotine varied widely with self-reports of exposure to ETS, but on average increased with increasing exposure. (*Am J Public Health* 1990; 80:988–990.)

Introduction

While health effects of passive smoking on children and adults have been identified, the principal location of exposure investigated has been the home.[1,2] Workplace exposure has received less attention, and health effects of environmental tobacco smoke (ETS) in the workplace remain controversial.

We enrolled 15 nonsmoking adults to determine the feasibility of measuring personal exposure to ETS at work and to characterize workplace exposures of this small group of subjects. Indicators of exposure, measured during a workday, included questionnaires, personal samples for respirable particles (RSP) and nicotine, and urinary and salivary cotinine.

Methods

Between October 1986 and May 1987, 15 nonsmoking volunteers (eight men, seven women), 18 years of age and older, were recruited from the Albuquerque, New Mexico area. We obtained exposure questionnaires, saliva, urine, and personal air particle samples during one workshift. The saliva and urine specimens were obtained before and after the workshift. Cotinine was quantitated by a double antibody radioimmunoassay, as described by Langone, *et al.*[3] Details of the assay in our laboratory have been reported previously.[4]

During the workshift, each subject wore a personal monitoring pump running at 1.7 l/min with a 10 mm nylon cyclone clipped to the shirt collar.[5] RSP samples were collected on 37 mm Fluropore filters (Millipore Corp). Nicotine was collected on a glass fiber backup filter treated with sodium bisulfate to minimize volatilization; after extraction from the filter, analysis for nicotine was done on a gas chromatograph with a flame ionization detector.[6] The recovery of nicotine by this procedure has been shown to be 98 percent efficient.

From the questionnaires, we derived measures of exposure including the total number of cigarette smokers and total number of hours exposed during the workshift. To describe the relationships among the measures of ETS exposure, Spearman correlations were calculated. Data analysis was performed with standard programs.[7]

Results

Occupations of the subjects were diverse (Table 1); mean age was 44.8 years; average duration of the workshift and of the personal monitoring was 6.5 hours (SD ± 2.0).

Exposure to cigarette smokers at work was reported by 13 of the 15 participants. Of the 13 reporting exposure, two reported exposure to crowds of smokers during their workshift and the remaining 11 encountered a mean of 8.8 smokers (SD ± 6.7). The mean reported hours of exposure was 3.4 (SD ± 2.1).

Respirable particle and nicotine concentrations varied widely with the reported number of smokers and hours of exposure. The mean concentrations for RSP and nicotine were 63.9 $\mu g/m^3$ (SD ± 41.5) and 20.4 $\mu g/m^3$ (SD ± 20.6), respectively. Correlations between the atmospheric markers

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TABLE 1—Description of Participants in a Personal Monitoring Study of Exposure to Environmental Tobacco Smoke at Work, New Mexico, 1986–87

Occupation/Workplace	Workshift Duration/ Exposure Duration (hours)	RSP ($\mu g/m^3$)	Nicotine ($\mu g/m^3$)
Males			
Physician/Hospital	8/5	52.3	10.0
Social Worker/Office	8/0	44.0	2.5
Stock Broker/Office	8/2	69.4	7.2
Bus Boy/Restaurant	8/8	145.8	45.0
Maintenance Worker/Retail Store	8/3	85.2	6.9
Barber/Barber Shop	8/0	14.7	4.0
Barber/Barber Shop	8/4	145.8	13.7
Volunteer/Hospital	4/2	80.0	46.0
Females			
Interviewer/Public Transportation	3/2	4.0	0.0
Travel Agent/Office	8/5	85.7	50.0
Travel Agent/Office	6/4	62.1	46.7
Attorney/Office	8/6	63.3	5.9
Volunteer/Hospital	4/3	27.6	6.3
Volunteer/Hospital	4/3	25.2	8.7
Volunteer/Hospital	4/4	53.2	53.2

and the questionnaire measures of exposure to ETS were moderate (Table 2).

As was observed for the atmospheric markers, the post-workshift urinary and salivary cotinine levels varied widely with self-reported exposure. In comparison with pre-workshift levels, post-workshift levels were not consistently increased. The mean pre-workshift urinary and salivary cotinine concentrations were 31.8 ng/mg Cr (SD ± 67.6) and 2.9 ng/ml (SD ± 5.0), respectively. For the post-workshift levels, the corresponding values were 19.7 ng/mg Cr (SD ± 43.2) and 3.5 ng/ml (SD ± 5.9).

Spearman correlation coefficients were calculated to examine the relations among the questionnaire variables, the atmospheric markers, and urinary and salivary cotinine (Table 2). Moderate correlations were obtained for self-reports and cotinine levels, and nicotine levels and cotinine levels. However, RSP levels and cotinine concentrations were not correlated.

TABLE 2—Spearman Correlations between Various Measures of Environmental Tobacco Smoke at Work, New Mexico, 1986–87

Correlated Measures	N	r
RSP ($\mu g/m^3$) with:		
Nicotine	15	0.57*
Total number of smokers	15	0.44
Total hours of exposure	15	0.53*
Postshift urinary cotinine	14	0.05
Postshift salivary cotinine	11	−0.07
Nicotine ($\mu g/m^3$) with:		
Total number of smokers	15	0.62*
Total hours of exposure	15	0.54*
Postshift urinary cotinine	14	0.60*
Postshift salivary cotinine	11	0.46
Postshift urinary cotinine (ng/mg Cr) with:		
Total number of smokers	14	0.39
Total hours of exposure	14	0.57*
Postshift salivary cotinine (ng/ml) with:		
Total number of smokers	11	0.63*
Total hours of exposure	11	0.45

*$p < 0.05$

Discussion

The controversial effects of involuntary smoking in the workplace need further investigation. The conduct of such research would be facilitated by the development of unintrusive and accurate methods of exposure assessment. Alternative approaches include active and passive monitoring, biological markers, and questionnaires. We have shown that personal monitoring for tobacco smoke components can be accomplished in the workplace. However, many employers and employees would not participate in the study because of concern about the wearing of pumps.

Despite the small number of subjects studied in this investigation, objective evidence of exposure to ETS was obtained in various workplaces. The levels of RSP and nicotine were similar to those observed in other investigations.[6,8–10] However, few of these studies included information on the intensity and duration of exposure to ETS.[10]

We observed moderate positive correlations among the questionnaire measures of ETS exposure, the results of personal monitoring for RSP and nicotine, and measurements of urinary cotinine. Each of these types of measures provides a differing index of exposure to ETS.[1] The questionnaire measures that were used assess source strength, but concentrations of ETS are also influenced by room volume and ventilation. Nicotine is a specific marker of exposure to ETS, whereas RSP is nonspecific. Cotinine levels reflect nicotine exposure, but also are determined by timing of specimen collection[10] and uptake and metabolism. Thus, tight concordance among these broad indicators of exposure used in this study would not be anticipated.

Because of the differing characteristics of questionnaires, personal monitoring, and biological markers for assessing ETS exposure, no single method should be considered as optimal for studying the workplace. We recommend that assessment of ETS exposure in indoor environments should utilize multiple approaches to characterize short- and long-term exposures. In population studies, questionnaire measures of exposure offer the simplest approach with personal atmospheric markers and biologic markers providing methods for estimating the potential magnitude of misclassification of self-reported exposure.

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Sexual Histories of Heterosexual Couples with One HIV-Infected Partner

NANCY S. PADIAN, MPH, PHD

Abstract: Ninety-eight heterosexual couples enrolled in a HIV transmission study, at least one of whom was HIV-infected, were interviewed about sexual behavior. Although males and females were interviewed separately, there was agreement between them on the number of sexual contacts, the practice or anal intercourse, and condom use. These findings of strong reliability are encouraging, but do not necessarily imply that the data are valid. (*Am J Public Health* 1990; 80:990–991.)

Introduction

The best way to prevent the spread of infection from human immunodeficiency virus (HIV) is voluntary behavioral change.[1] Before recommending strategies to promote such changes, one must first establish the kinds of behavior currently practiced. To do so, AIDS (acquired immunodeficiency syndrome) researchers rely almost exclusively on interviewing techniques, but many question the validity and reliability of this methodology.[2] For example, in a study of the reproductive histories of a group of women, Hornsby and Wilcox[3] established that daily logs of sexual behavior were more accurate than comparable data collected through retrospective interviews. Similar results were found by both Udry and Morris[4] and Kunin and Ames,[5] who determined that recent and frequent reporting of sexual behavior produced the most precise results. However, AIDS epidemiologists may not have the opportunity to collect data on a regular basis and are thus forced to rely on retrospective reports of behavior even though the accuracy of these reports (especially for a variety of sexual practices) has not been established. Here I report on the reliability of such data, comparing reports of sexual behavior between men and women in couples of which at least one partner was HIV seropositive.

Methods

Since 1985 we have been conducting a study of the heterosexual transmission of acquired immunodeficiency syndrome (AIDS) in California in which we enroll the opposite sex partners of individuals infected with HIV. Although the study began by enrolling the female partners of HIV-infected men,[6] in 1987 we began to enroll participants as couples. Individuals who test positive for HIV at a variety of sites and who also have heterosexual partners are referred to the study as part of their post-test counseling. Enrollment is voluntary; study protocol is described elsewhere.[6]

Interviewers are female and are matched to couples by ethnicity. They are trained in group and individual sessions that include role playing and interpretation of interview responses. Results were reliable across interviewers. To ascertain number of sexual contacts, the interviewer asks how many times the couple has sexual intercourse in a typical week or month. Deviations from this number throughout the relationship are noted. The total number of contacts is estimated by multiplying the duration of the relationship by the typical reported amount and weighting this number by changes in sexual activity over time. Individuals in the couple are interviewed separately on the same day.

Behaviors considered in this report are: vaginal intercourse, anal intercourse, and condom use. Continuous responses were compared using Pearson's correlation coefficient, and categorical responses were compared using the Kappa coefficient and its corresponding confidence limits as described by Fleiss.[7] HIV infection was ascertained from serological tests using enzyme immunoassays with Western Blot confirmation.

Results

This report includes data from 98 couples, 68 percent of which were monogamous at entry into the study. Most of the men and women reported only one partner in the six months prior to entry into the study. Median number of partners since 1978 (the beginning of the AIDS epidemic) was five for the women and 10 for the men. The overall male-to-female transmission rate from the study which began in 1985 was 24 percent. Seventy-seven of the couples included infected men and their female partners; 12 (16 percent) of these women were infected. Twenty-one of the couples were infected women and their male partners; none of these men were infected. The reported risk group of the infected partner of the 98 couples varied and is described in Table 1. Sixty-three percent of the couples were White, 20 percent Latino, 7 percent Black, 1 percent Asian, and the remainder were couples of mixed ethnicity. Average income for the couples was $20–29,000 per year; average level of education was 13

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Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home[1–4]

DAVID B. COULTAS,[5] JONATHAN M. SAMET, JOHN F. MCCARTHY, and JOHN D. SPENGLER

SUMMARY We assessed the variability of four markers of environmental tobacco smoke exposure in 10 homes with 20 nonsmoking and 11 smoking household members. We obtained exposure questionnaires, saliva and urine for cotinine, and air particle samples for respirable particles and nicotine on 10 sampling days: every other day over 10 days, and then 1 day every other week over 10 wk. The mean concentrations of respirable particles in the 10 homes ranged from 32.4 to 78.9 $\mu g/m^3$, and concentrations of nicotine ranged from 0.6 to 6.9 $\mu g/m^3$. Linear regression models that included indicator variables for self-reported exposure explained 9 and 6% of the variability of the respirable particle and the nicotine concentrations, respectively. The individual mean urinary cotinine levels standardized to creatinine concentration ranged from 3.9 to 55.8 ng/mg Cr, and for salivary cotinine the mean levels ranged from 0.9 to 4.3 ng/ml. Indicator variables for self-reported exposure explained 8 and 23% of the variability of the urinary and salivary cotinine levels, respectively. We conclude that because of the marked variability of these measures, multiple measurements are needed to establish a stable profile of exposure to environmental tobacco smoke in the home.

AM REV RESPIR DIS 1990; 142:602–606

Introduction

Numerous epidemiologic investigations have examined the adverse effects of passive smoking on children and adults; the evidence is sufficiently compelling to establish passive smoking as a cause of disease in nonsmokers (1, 2). Both the 1986 Surgeon General's Report (1) and the National Research Council (2) have concluded that passive smoking causes increased lower respiratory illness in infants, increased respiratory symptoms in children, reduced lung growth during childhood, and lung cancer in nonsmokers. Although health effects of passive smoking have been convincingly demonstrated, additional research is needed to address unresolved issues concerning this preventable exposure. For example, more precise description of exposure-response relations should be achieved for the already established health effects. Uncertainties concerning the adverse effects of passive smoking in the workplace and on the occurrence of ischemic heart disease must also be resolved.

The conduct of this research would be facilitated by improved methods for exposure assessment. In most epidemiologic studies on passive smoking published to date, exposure to environmental tobacco smoke, the combination of exhaled mainstream smoke and sidestream smoke, has been assessed by questionnaire. However, exposure to environmental tobacco smoke can also be estimated with air monitoring and measurement of biologic markers in body fluids, such as salivary cotinine. Biologic markers are increasingly emphasized as a standard for validating questionnaire responses. To characterize the relationships among these alternative approaches for assessing passive smoking in the home environment, we conducted a prospective study of 10 households. We periodically collected questionnaire information on exposure and measured respirable particles and nicotine in air samples and urinary and salivary cotinine in the 20 nonsmokers in these households.

Methods

Sample Selection

Between February and December 1986, 149 nonsmoking volunteers, 18 years of age and older, were recruited from Albuquerque and surrounding communities to participate in a study of the accuracy of questionnaire assessment of exposure to environmental tobacco smoke (3). From this sample, we selected 10 subjects living with at least one cigarette smoker and requested the participation of the entire household for this investigation. The households were selected on the basis of willingness to participate and location, and were not intended to be representative of the original sample.

Data Collection

Between March and October 1986, we obtained exposure questionnaires, saliva and urine, and air particle samples on 10 sampling days: every other day over 10 days, and then 1 day every other week over 10 wk. The questionnaires and saliva and urine specimens were obtained at the end of a 24-h air monitoring period (described below). From the questionnaires, we determined the reported number of smokers and number of hours that the subjects were exposed during the previous 24 h to cigarettes, cigars, and pipes at home, at work or school, in a vehicle, and in other places. Questionnaires were self-completed by the adults, and by a parent for children 14 years of age and younger. Spot saliva and urine specimens were obtained and frozen at −20° C until the cotinine assays were performed.

Cotinine Assay

Cotinine was quantitated by a double antibody radioimmunoassay, as described by Langone and coworkers (4). A specific antiserum produced in rabbits was supplied by Dr. Helen Van Vunakis (Brandeis University). Urine samples were diluted 1:4 for the assay. The sensitivity of the assay in our hands was 36 pg/tube or 0.78 ng/ml of urine (4,204 pmol/L). Urine creatinine concentrations were determined by the Jaffe reaction (5), and the cotinine concentrations were standardized to the creatinine concentrations. Assays were performed without knowledge of questionnaire responses.

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[2] Supported by Grant No. EPA CR811650 from the Environmental Protection Agency.

[3] Presented in part at the Air Pollution Control Association Specialty Conference on Combustion Processes and the Quality of the Indoor Environment, Niagara Falls, New York, September 1988.

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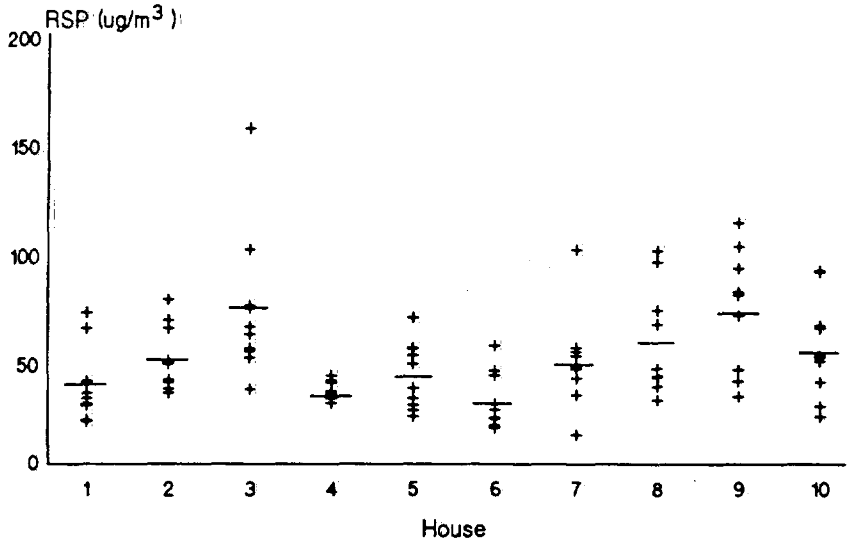

Fig. 1. Respirable particle concentrations (RSP) measured during 24-h sampling periods in 10 homes with at least one cigarette smoker. The bars indicate the mean levels for each home.

Particle Measurements

In the major activity room of each home, Harvard School of Public Health impactors (6), operating at a flow rate of 4 L/min, were used to collect respirable particles and gaseous nicotine samples. Through a timed solenoid switching valve, two impactors used a common, mass-flow controlled pump, and each impactor operated on alternate 15-min collection cycles. Respirable particle samples, 2.5 µm in diameter or less, were collected on Teflon® filters (Membrana, Inc., Pleasanton, CA), and nicotine was collected on sodium-bisulfate-treated glass fiber filters (Millipore Corp., Bedford, MA) to minimize its volatilization. After extraction from the filter, analysis for nicotine was done on a Shimadzu GC7A gas chromatograph (Columbia, MD) with a flame ionization detector. The nicotine collection and extraction procedure is a modification of that described by Hammond and coworkers (7). The recovery of nicotine by this procedure has been shown to be 98% efficient. The sensitivity for detection of respirable particles and nicotine was 5.0 µg and 0.05 ppm, respectively.

Data Analysis

Variability of questionnaire responses, respirable particle and nicotine concentrations, and urinary cotinine levels were assessed with univariate analyses. From the questionnaire responses, we used the total number of household smokers, including cigarette, cigar, and pipe smokers, and the total number of hours exposed as the measures of home exposure. The predominant source of tobacco smoke was from cigarette smoking. During the entire sampling period, there were only 4 days in which any subject reported exposure to a cigar smoker, and none reported exposure to a pipe smoker.

To examine determinants of the variability in the measurements, we used multiple linear regression. The dependent variables (respirable particles, nicotine, urinary cotinine, and salivary cotinine) were analyzed as continuous variables. For the predictive factors, indicator variables were defined for house (HOUSE = 1 to 10), individual (INDIVIDUAL = 1 to 20), age group (AGE GROUP < 18 yr versus ≥ 18 yr), season (SEASON = March-April versus May-October), and number of smokers per day (NUMBER = zero versus ≥ 1). Other independent variables, number of hours (HOURS) exposed per day, respirable particles, and nicotine were continuous.

Data analyses were performed with standard programs of the Statistical Analysis System (8).

Results

The 10 households included 11 cigarette smokers and 20 nonsmokers, 11 females and nine males 1.5 to 74 yr of age. The homes included eight unattached single family houses, one mobile home, and one apartment.

Reports on exposure to tobacco smoke in the home were obtained for all 10 sampling days from 17 subjects, and for 9 days from three subjects. The reported number of cigarette smokers in the home per day did not vary widely. The median number (range) of smokers per day was one for 18 of the nonsmoking subjects (zero to 10), zero for one subject (zero to 1), and four for one subject (2 to 25). Greater variability was reported for the number of hours exposed to cigarette smoke in the home, with the median number of hours ranging from zero to 11 h.

Respirable particle and nicotine concentrations were obtained for 99% of the sampling days (figures 1 and 2). The mean concentrations of respirable particles in the 10 homes ranged from 32.4 µg/m³ (SD = 13.1) to 76.9 µg/m³ (SD = 32.9), and concentrations of nicotine ranged from 0.6 µg/m³ (SD = 0.69) to 6.9 µg/m³ (SD = 8.2). Spearman's correlation coefficient between the respirable particle concentrations and the nicotine concentrations was 0.54 (n = 99, p = 0.0001).

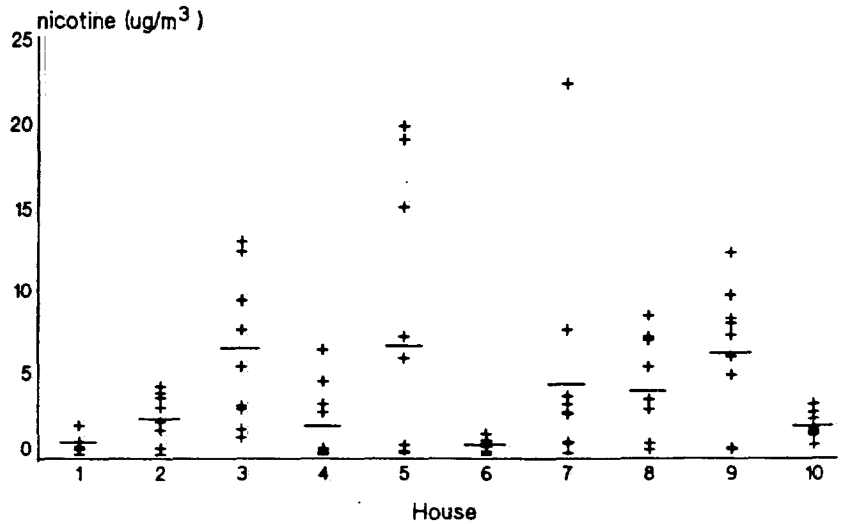

Fig. 2. Atmospheric nicotine concentrations measured during 24-h sampling periods in 10 homes with at least one cigarette smoker. The bars indicate the mean levels for each home. Levels of nicotine were undetectable on 1 or more days in Houses 1 (n = 3), 2 (n = 2), 4 (n = 2), and 6 (n = 1).

TABLE 1

COEFFICIENTS OF DETERMINATION FOR THREE LINEAR REGRESSION MODELS* PREDICTING RESPIRABLE PARTICLE AND NICOTINE CONCENTRATIONS IN AIR SAMPLES FROM 10 HOMES, NEW MEXICO, 1986

	R^2		
Dependent Variable	Model 1	Model 2	Model 3
Respirable particles, $\mu g/m^3$	0.34	0.08	0.09
Nicotine, $\mu g/m^3$	0.28	0.04	0.06

* Independent variables: Model 1 = HOUSE (1 to 10, representing the 10 homes); Model 2 = NUMBER (zero versus ≥ 1 smokers) + SEASON (March–April versus May–October); Model 3 = NUMBER (zero versus ≥ 1 smokers) + HOURS (continuous) + SEASON (March–April versus May–October).

TABLE 2

REGRESSION COEFFICIENTS FOR MODEL THREE* PREDICTING RESPIRABLE PARTICLE AND NICOTINE CONCENTRATIONS IN AIR SUPPLY FROM 10 HOMES, NEW MEXICO, 1986

	Regression Coefficients for Model 3		
	One or More Smokers	HOURS	Cold Months
Respirable particles, $\mu g/m^3$	+17.3 (−3.0, 37.7)†	+0.4 (−1.0, 1.8)	+8.9 (−1.1, 18.9)
Nicotine, $\mu g/m^3$	+2.1 (−2.7, 5.9)	+0.2 (−0.1, 0.5)	−0.7 (−2.5, 1.1)

* See text and table 1 for description of Model 3.
† 95% confidence intervals shown in parentheses.

The variability of respirable particle and nicotine concentrations for the two sampling periods, every other day or every other week, were described with one-way analysis of variance. For the respirable particle concentrations, the intrahouse mean square error, describing the extent of variation for a particular household, was greatest for sampling every other day (516.8) compared with every other week (258.7). A contrasting pattern of variation was observed for nicotine, with mean square errors of 3.6 and 19.0 for every other day and every other week, respectively.

For the particle and nicotine measurements, we used linear regression to examine factors influencing the concentrations and the variability of the concentrations. A model that included variables representing each of the 10 houses explained the greatest amount of variability, as shown by the magnitude of the R^2 value (table 1). Compared with the model with the variables for individual homes, the models that included number of smokers explained markedly lower percentages of the variability of levels of nicotine and particles. Although not statistically significant, increases in respirable particles were associated with exposure to one or more cigarette smokers in the home and with the colder months, March and April (table 2). There was no association of particle levels with the number of hours of exposure. Nicotine levels increased, although not significantly, with exposure to smokers in the home, but were not predicted by the season (table 2).

Cotinine levels were obtained on 187 urine specimens from 20 nonsmokers, and 153 saliva specimens were obtained from 16 nonsmokers. We were unable to obtain saliva specimens from four children, all 4 yr of age or younger. The individual mean urinary cotinine levels standardized to urinary creatinine concentration ranged from 3.9 ng/mg Cr (SD = 6.5) to 55.8 ng/mg Cr (SD = 32.0). For salivary cotinine, the mean levels ranged from 0.9 ng/ml (SD = 0.8) to 4.3 ng/ml (SD = 1.4). The mean urinary cotinine levels and variability tended to be greater in the children than in the adults (figures 3 and 4) (data not shown for salivary cotinine). Spearman's correlation between the urinary cotinine and salivary cotinine concentrations was 0.32 (n = 153, p = 0.0001). Correlations between the cotinine levels and the atmospheric markers were highest for salivary cotinine and nicotine (table 3).

As for the atmospheric markers, we

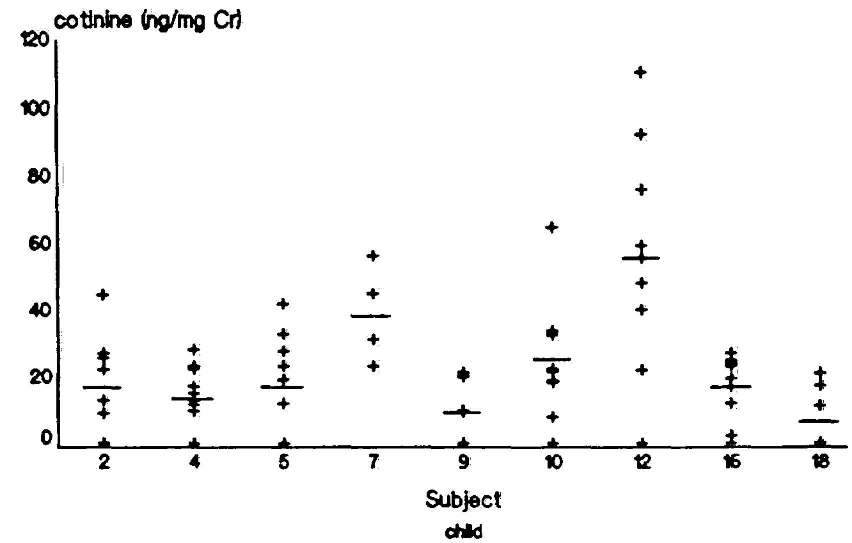

Fig. 3. Urinary cotinine concentrations standardized to urinary creatinine concentration in nine nonsmoking children from homes with at least one cigarette smoker. The bars indicate the mean levels for each child. Levels of urinary cotinine were undetectable on 1 or more days for Subjects 2 (n = 2), 4 (n = 2), 5 (n = 3), 9 (n = 4), 10 (n = 1), 12 (n = 1), 16 (n = 1), and 18 (n = 5).

TABLE 3

SPEARMAN'S CORRELATION COEFFICIENTS BETWEEN COTININE LEVELS IN URINE AND SALIVA AND RESPIRABLE PARTICLES AND NICOTINE, NEW MEXICO, 1986

	r
Urinary cotinine, n = 187	
Respirable particles	0.25
Nicotine	0.15
Salivary cotinine, n = 153	
Respirable particles	0.25
Nicotine	0.38

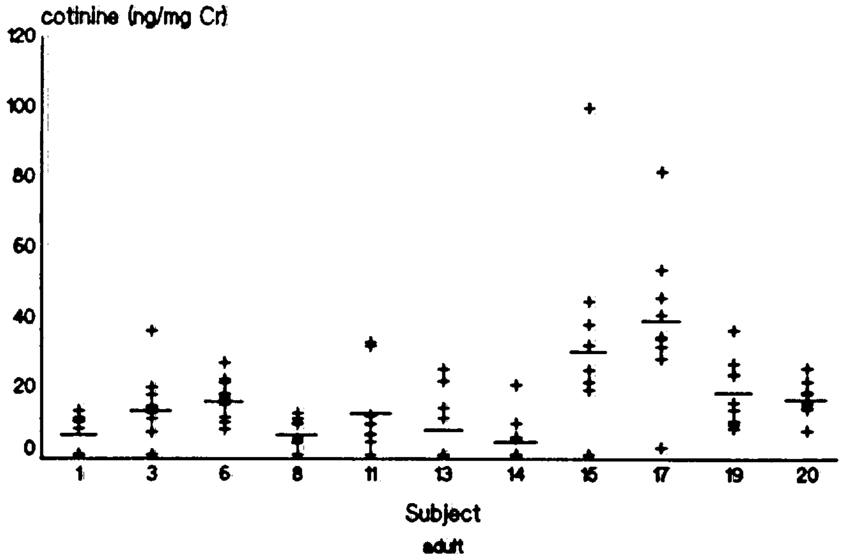

Fig. 4. Urinary cotinine concentrations standardized to urinary creatinine concentration in 11 nonsmoking adults from homes with at least one cigarette smoker. The bars indicate the mean levels for each adult. Levels of urinary cotinine were undetectable on 1 or more days for Subjects 1 (n = 4), 3 (n = 2), 8 (n = 2), 11 (n = 1), 13 (n = 6), 14 (n = 6), and 15 (n = 2).

TABLE 4

COEFFICIENTS OF DETERMINATION FOR THREE LINEAR REGRESSION MODELS* PREDICTING URINARY AND SALIVARY COTININE CONCENTRATIONS IN NONSMOKERS EXPOSED TO TOBACCO SMOKE, NEW MEXICO, 1986

	R^2		
Dependent Variable	Model 1	Model 2	Model 3
Urinary cotinine, ng/mg Cr	0.47	0.05	0.08
Salivary cotinine, ng/ml	0.57	0.09	0.23

* Independent variables: Model 1 = INDIVIDUAL (1 to 20, representing the 20 nonsmoking individuals); Model 2 = NUMBER (zero versus $\geq$ 1 smokers) + SEASON (March–April versus May–October) + AGE GROUP (< 18 versus $\geq$ 18 yr); Model 3 = NUMBER (zero versus $\geq$ 1 smokers) + HOURS (continuous) + SEASON (March–April versus May–October) + AGE GROUP (< 18 versus $\geq$ 18 yr).

used one-way analysis of variance to describe the variability in urinary and salivary cotinine concentrations during the two sampling periods: every other day or every other week. In contrast to the atmospheric markers, the variability in cotinine levels was comparable for the two periods. The intraindividual mean square errors for urinary cotinine were 175.8 and 194.8, and for salivary cotinine it was 0.9 and 0.7.

For the urinary and salivary cotinine levels, we also examined determinants of variability and concentration with linear regression. Models that included indicator variables for the 20 nonsmoking subjects explained 47 and 57% of the variability in cotinine levels, respectively (table 4). Compared with this model, other models that included exposure to environmental tobacco smoke and age group explained much lower proportions of the variability. Urinary cotinine levels were significantly ($p < 0.05$) higher among children than among adults (table 5). Although the effect was not significant, exposure to one or more smokers resulted in higher urinary cotinine levels than did no exposure. The number of hours of reported exposure and the season were not significant predictors of cotinine level. For salivary cotinine level, the hours of exposure was the only significant predictor.

Prediction of level of urinary or salivary cotinine was not greatly improved with the use of respirable particles or nicotine as independent variables. The proportions of the variability in the urinary cotinine levels explained by respirable particle and nicotine concentrations were 0.03 and 0.04, respectively. For salivary cotinine, the corresponding R^2 values were only slightly higher at 0.07 and 0.13, respectively.

Discussion

Environmental tobacco smoke is a complex mixture of gases and particles that changes as it ages. Personal exposure to environmental tobacco smoke is determined by the nonsmoker's activity pattern; exposure may be received in the diverse microenvironments encountered throughout the course of day-to-day activities. For many nonsmokers, the home is a predominant location of exposure (9). In this investigation, we assessed methods for measuring exposure to environmental tobacco smoke in the home that can be used for epidemiologic research: air monitoring, questionnaires, and biologic markers.

In other populations, cigarette smok-

TABLE 5

REGRESSION COEFFICIENTS FOR MODEL THREE* PREDICTING URINARY AND SALIVARY COTININE CONCENTRATIONS IN NONSMOKERS EXPOSED TO TOBACCO SMOKE, NEW MEXICO, 1986

	Regression Coefficients* Model 3			
	One or More Smokers	HOURS	SEASON	AGE GROUP
Urinary cotinine, ng/mg Cr	+5.4 (−4.8, 15.6)†	+0.8 (0.0, 1.6)	−0.2 (−5.8, 5.4)	+5.4 (0.0, 10.8)
Salivary cotinine, ng/ml	+0.13 (−0.06, 0.86)	+0.15 (0.09, 0.21)	−0.02 (−0.41, 0.37)	−0.81 (−1.34, −0.28)

* See text and table 4 for description of Model 3.
† 95% confidence intervals shown in parentheses.

ing has been shown to be a strong source of respirable particles in the home (1, 10, 11). Spengler and coworkers (10) estimated that the average increase in the indoor concentration of respirable particles was 20 $\mu g/m^3$ for each smoker. We estimated an average increase of 17 $\mu g/m^3$ for one or more smokers (table 2); the average concentrations in the New Mexico homes (figure 1) were above the mean of 24 $\mu g/m^3$ in nonsmoking homes from six U.S. cities (10). Nicotine was present on most sampling days (figure 2). The moderate correlation between the nicotine and respirable particle concentrations (Spearman's $r = 0.54$) confirms the importance of tobacco smoking as a source of particulate pollution in the home. Little data have been reported on nicotine concentrations in the home (1, 2); the levels in the New Mexico homes were somewhat lower than an average concentration of 11.2 $\mu g/m^3$ reported by Muramatsu and coworkers (12) for three homes in Japan. However, the results from our investigation and the Japanese study are not directly comparable because the Japanese data were from personal samples. Furthermore, information on intensity or duration of exposure to tobacco smoke was not provided for the Japanese homes. In a recent study in North Carolina, the homes of 27 children were monitored overnight for nicotine with a sampler that was located near the child (13). The average nicotine concentration in homes with smokers was 3.74 $\mu g/m^3$, with a range from about 1 to 7 $\mu g/m^3$. The higher levels in our study may reflect the differing sampling strategies; the nicotine sampler remained in the activity room throughout the monitoring period in our study, but it was moved to the child's bedroom in the North Carolina study when the child slept.

Questionnaires on exposure to environmental tobacco smoke generally assess the strength of the source, e.g., the number of smokers or the number of cigarettes consumed, and the duration of exposure. The concentration of environmental tobacco smoke, however, depends not only on the source strength but on room size, mixing, adsorption of smoke components, and the rate of exchange of indoor with outdoor air. Personal exposure also varies with the nonsmoker's proximity to the smoker. Questionnaires cannot comprehensively and accurately assess each of these factors.

Not surprisingly, we found that the questionnaire responses were poor predictors of concentrations of respirable particles and nicotine (table 1). The highest R^2 values were obtained with a regression model that included variables for the individual homes; presumably, these variables represented characteristics of the homes, many of them unmeasurable, that determined concentrations at a given level of smoking.

Cotinine, nicotine's major metabolite, has a half-life of 20 to 40 h in nonsmokers (1). It can serve as a specific biologic marker of exposure to environmental tobacco smoke that has been received over a period of days. At any given level of nicotine exposure, cotinine levels in body fluids are also determined by uptake, metabolism, and excretion (1). In regression analyses to predict cotinine concentrations, the models that included variables for the individual subjects gave the highest R^2 values (table 4). Models including only the questionnaire-derived exposure measures or the atmospheric markers had low R^2 values. Our findings in a large population-based survey were similar (14). In 247 nonsmoking adults with a detectable cotinine level, variables for subject age, number of cigarettes smoked by the spouse, and number of cigarettes smoked by other household smokers explained only 2% of the variance of salivary cotinine level for females, and 16% of the variance for males.

In epidemiologic investigations of the adverse health effects of environmental tobacco smoke, questionnaires have been the sole approach for assessing exposure (1, 2). Air monitoring and biologic markers represent promising and feasible approaches for assessing exposure to environmental tobacco smoke. For the home environment, our data demonstrate that indexes of exposure to environmental tobacco smoke based on questionnaires, biologic markers, and air monitoring are not tightly correlated. At a particular level of exposure, as assessed by inventory of household smokers, concentrations of respirable particles and nicotine vary widely, as do levels of salivary and urinary cotinine. The variability of the atmospheric and biologic markers must be considered in using them as standards for assessing misclassification by questionnaires. For environmental tobacco smoke exposure at home, our data suggest that single measurements of either levels of environmental tobacco smoke components or of biologic markers are not adequate for characterizing usual exposure. Multiple measurements are needed. It may be misleading to assess the validity of questionnaire measures against a single determination of an atmospheric or biologic marker. We suggest that atmospheric and biologic markers offer complementary approaches to questionnaires for assessment of exposure to environmental tobacco smoke, and that these methods should be used together to estimate the magnitude of misclassification from questionnaire responses.

Acknowledgment

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LETTER TO THE EDITOR

IMPLICATIONS FOR DISEASE MISCLASSIFICATION IN EPIDEMIOLOGICAL STUDIES OF LUNG CANCER RISK FOR NONSMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE

Dear Editor:

The U. S. Environmental Protection Agency (EPA) appears to have diminished or dismissed the potentially significant role of disease misclassification in its review of lung cancer risk in nonsmokers reportedly exposed to environmental tobacco smoke (ETS). After reviewing 31 epidemiological studies of lung cancer risk in nonsmokers married to smokers v. those married to nonsmokers (USEPA 1992), EPA concluded that the statistics support the conclusion of a significant risk for nonsmokers exposed to ETS. Adjustments were made for potential misclassification of smoker status, but EPA made no attempt to adjust for potential disease misclassification, which is more likely to result in overestimation than underestimation of relative risk.

Disease misclassification arises when "lung cancer cases" are not primary lung carcinomas but are secondary cancers that have metastasized to the lung from primary tumors originating in other body tissues. Definitive diagnosis of primary lung cancer requires histological or cytological examination of lung tissue.

Diagnoses based on other than histological or cytological examination are equivocal, at best. American Cancer Society researchers noted (Garfinkel et al. 1985) one U.S. study in which 13% of hospital cases were found to be improperly identified as primary lung cancers.

The EPA Review Draft acknowledges the possibility of disease misclassification in epidemiological studies, commenting that it creates "bias toward the null" without further explanation or acknowledgement that such bias is not consistent in the direction of bias nor in magnitude from study to study.

Relative risk in epidemiological studies is determined from the data arrayed as follows:

Lung Cancer Present	ETS Exposed	
	Yes	No
Yes	a	b
No	c	d

with the odds ratio for case-control studies calculated from the formula, $OR = ad/bc$, and the relative risk for cohort or prospective studies from the formula, $RR = (a/a+c)/(b/b+d)$. (For editorial simplicity, the term relative risk is often used for both kinds of studies and determinations.)

The potential effect of disease misclassification can be illustrated in the study of Hirayama (1984) in Japan, which was among the earliest of the epidemiological assessments said to find lung cancer risk in nonsmokers married to smokers. Hirayama (1984), along with the early Greek study (Trichopoulos et al. 1981) were the only studies in the data bases of the National Research Council (NRC 1986) and the Surgeon General's (USSG 1986) reports to claim statistically significant increased risk for nonsmokers married to smokers.

The Hirayama study was based on 91 540 death certificates, of which 200 reportedly were for nonsmokers who had died of lung cancer. Twenty-one (10.5%) of the certificates reported cause of death determined by autopsy, but the type of lung cancer was not specified, and there is no basis for believing that many were histologically or cytologically confirmed as primary lung carcinomas. For the remaining 179 (89.5%) cases, no basis for the classification of death was reported, indicating that at least 89% and up to 100% of the lung cancer cases in Hirayama's study are of questionable disease classification. The Surgeon General's Report (USSG 1986) noted the potential for disease misclassifica-

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tion with the comment that "Hirayama was unable to assess the accuracy of the diagnoses listed on the death certificate[s]."

Assessing the Hirayama data from the following array

Lung Cancer Present	ETS Exposed	
	Yes	No
Yes	163	37
No	69 482	21 858

EPA (USEPA 1992) reported a crude relative risk of 1.38 (90% C.I. 1.03-1.87). There is potential disease misclassification, however, for all 200 lung cancer cases, with more than four and one-half times as many cases among those exposed to ETS than among those not exposed.

If as few as four of the 163 lung cancer cases exposed to ETS were disease misclassified—i.e., were not primary lung carcinomas—the relative risk would be a statistically nonsignificant 1.34 (C.I. 0.99-1.71).

Of the 31 epidemiological studies in the data base of the EPA Review Draft, all lung cancer cases of 12 studies were reported to have been histologically or cytologically confirmed. In 14 studies, from 2% to 100% of the lung cancer cases had not been definitively confirmed, while in 5 studies, the method and extent of verification were not reported.

Among the 27 case-control studies, ten had 10% or more of lung cancer cases not definitively confirmed as primary carcinomas, including 45 (83%) of 54 cases in the Liu study, 40 (43%) of 94 cases in Akiba, 14 (35%) of 40 cases in Trichopoulos, 108 (26%) of 417 cases in Wu-Williams, and 46 (19%) of 246 cases in Gao, for a total of 253 (30%) of 851 "lung cancer cases" not confirmed as primary. For all case-control studies where the extent of diagnosis confirmation was established, EPA data show 302 lung cancer cases were not definitively confirmed.

Of the cohort or prospective studies, none of the 200 lung cancer cases in the Hirayama study were known to have been confirmed as primary, and the Review Draft notes the absence of information on the other three cohort studies. It also notes that in 10 studies "secondary lung cancers" had not been excluded.

The EPA Review Draft shows 64% of the cases were classified as exposed to ETS, so that there may be nearly twice the likelihood of disease misclassification among "cases" classified as exposed to ETS as among those not exposed. However, any assumptions about the distribution of disease misclassifications in specific studies or in the overall data base would be entirely speculative and insupportable.

The failure to give appropriate consideration in the EPA Review Draft to the significant potential for disease misclassification reduces confidence in risk estimates derived from the data and raises serious questions about public health policies based on such studies.

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This review was conducted at the request of The Tobacco Institute; the statements expressed herein are solely those of the author.

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Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?

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Summary

Combined evidence from at least 15 epidemiological cohort and case-control studies appears to indicate non-smokers married to smokers have a risk of lung cancer 30%–40% higher than that of non-smokers married to non-smokers. This increase is surprisingly large, given the very low level of exposure to smoke constituents of non-smokers compared with that of smokers. The possibility that it results wholly or in part from bias, rather than as a direct effect of exposure to environmental tobacco smoke (ETS), must be considered seriously. Weaknesses of much of epidemiological evidence and the various possible sources of bias are discussed in detail.

One serious potential source of bias arises if even a small proportion of smokers are misclassified as non-smokers. Data from a series of studies specifically designed to determine accuracy of statements on current smoking habits (by salivary cotinine measurements) and on past smoking habits by repeated questionnaires) suggests that such misclassification might cause bias large enough to explain a major part, and perhaps all, of the apparent increase in lung cancer risk related to spouse smoking. Whilst evidence from a detailed review of the available literature on misclassification of smoking habits, is consistent with this view, there is a need for more research on this issue. Future epidemiological studies on passive smoking and lung cancer need to obtain more objective and reliable information on the subject's smoking habits and exposure to ETS. Bias can also arise if positive studies are more likely to be reported than negative studies and research is needed to attempt to estimate the extent of this bias.

Data currently available do not permit reliable conclusions to be drawn concerning the relationship of ETS exposure to lung cancer risk.

The Association

Since the early studies of Hirayama (1981) and Trichopoulos et al. (1981) reporting that never smokers married to smokers have a higher risk of lung cancer than those married to non-smokers, further epidemiological evidence has accumulated. Table 1 summarizes evidence from 16 published studies, 1–3 being prospective studies and 4–16 case-control studies. Wald et al. (1986), based on results from studies 1–13, reported an overall significant relative risk of 1.35, with 95% confidence limits of 1.19–1.54. This estimate is in broad agreement with other estimates of 1.30 (Lee 1984), 1.41 (Wells 1986) and 1.2–1.5 (Doll 1986). It would not be materially affected by including results from studies 14–16 of Table 1 since they are all small, and have relative risks that vary either side of the average.

While the overall evidence, which is based on a total of almost 1,200 lung cancer deaths in never smokers, predominantly in females, suggests a statistically significant

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Table 1. Summary of epidemiological studies of risk of lung cancer in never smokers in relation to environmental tobacco smoke exposure

Study number	Authors	Study location	Sex	Number of lung cancers[a]	Relative risk	Significance[b]
1	Hirayama (1981, 1984)	Japan	F	163	1.63	Yes
			M	64	2.25	Yes
2	Garfinkel (1981)	USA	F	153	1.17	No
3	Gillis et al. (1984)	Scotland	F	8	1.00	No
			M	6	3.25	No
4	Trichopoulos et al. (1981, 1983)	Greece	F	77	2.11	Yes
5	Chan and Fung (1982)	Hong Kong	F	84	0.75	No
6	Correa et al. (1983)	USA	F	22	2.07	(Yes)
			M	8	2.00	No
7	Buffler et al. (1984)	USA	F	41	0.78	No
			M	11	0.52	No
8	Kabat and Wynder (1984)	USA	F	24	0.79	No
			M	12	1.00	No
9	Koo et al. (1984, 1987)	Hong Kong	F	88	1.64	No
10	Garfinkel et al. (1985)	USA	F	134	1.31	(Yes)
11	Akiba et al. (1986)	Japan	F	94	1.50	No
			M	19	1.80	No
12	Lee et al. (1986)	England	F	32	1.00	No
			M	15	1.30	No
13	Pershagen et al. (1987)	Sweden	F	67	1.20	No
14	Wu et al. (1985)	USA	F	29	1.20	No
15	Ziegler (in Delager et al. (1986))	USA	M	16	<1	No
16	Humble et al. (1987)	USA	F	20	1.80	No
			M	8	>1.80	No

[a] Among never smoking subjects
[b] Yes = significant at 95% confidence level in comparison of exposed and non-exposed subjects; (Yes) = significance only in trend analysis or in subjects exposed to heavy smokers

association, it is not at all clear that it represents a causal effect of exposure to environmental tobacco smoke.

Before coming to any conclusion it is necessary to consider two important questions:

(a) Is the magnitude of the association plausible, in view of what is known about the epidemiology of active smoking and the relative levels of smoke constituents to which smokers and non-smokers are exposed?
(b) Is the epidemiological evidence open to any serious bias which might affect relative risk estimates in specific studies, or generally?

Table 2. Comparison of relative risks of lung cancer in relation to passive and active smoking

Study number	Authors	Sex	Relative risk		Ratio of excess risk
			Passive	Active	
1	Hirayama (1981, 1984)	F	1.63	3.81	0.22
		M	2.25	4.91	0.32
3	Gillis et al. (1984)	F	1.00	1.53	0.00
		M	3.25	5.92	0.46
4	Trichopoulos et al. (1981, 1983)	F	2.08	2.90	0.57
5	Chan and Fung (1982)	F	0.75	3.07	−0.12
6	Correa et al. (1983)	F	2.07	18.51	0.06
		M	2.00	18.27	0.06
7	Buffler et al. (1984)	F	0.78	5.37	−0.05
		M	0.52	5.26	−0.11
9	Koo et al. (1984, 1987)	F	1.64	3.80	0.23
11	Akiba et al. (1986)	F	1.50	3.36	0.21
		M	1.80	3.55	0.31
12	Lee et al. (1986)	F	1.00	4.75	0.00
		M	1.30	12.91	0.03
14	Wu et al. (1985)	F	1.20	4.50	0.06

Plausibility

Table 2 compares relative risks of lung cancer in relation to passive and active smoking. The passive smoking estimates compare risk in never smokers according to whether or not they are married to a smoker, while the active smoking estimates compare ever smokers and never smokers. Exceptionally, in studies 1 and 3, the comparison is in relation to current rather than ever smoking. The table also shows the ratio of excess risk in relation to passive and active smoking. Nine of the 16 ratios suggest an effect of passive smoking 6% or less than that of active smoking, while seven suggest an effect 20% or more. Overall the epidemiological data appear to be indicating that passive smoking has 10–15% of the effect of active smoking. Most studies of active smoking suggest a linear relationship between lung cancer risk and number of cigarettes smoked per day, though a quadratic relationship has been proposed (Doll and Peto 1978). It follows that if the epidemiological data are unbiased one would expect that the average dose received from passive smoking is at least 10%–15% of that from active smoking.

Many workers have used the (virtually) tobacco specific marker cotinine as an indicator of exposure of passive and active smokers. Table 3, based on an extensive UK study by Lee (1987) which will be referred to in more detail below, found that the increase in salivary cotinine in relation to passive smoking was less than 1% of that in relation to active smoking. Similar findings have been reported by other workers (e.g. Jarvis et al. 1984). The only study reporting relative levels much higher than this (Matsukura et al. 1984) has been questioned (Adlkofer et al. 1985; Pittenger 1985).

Since lung cancer risk in smokers is generally thought to be related to particulate matter rather than nicotine, it can be argued that an index of relative exposure of passive

Table 3. Salivary cotinine levels in relation to active and passive smoking

Exposure	Sex	Salivary cotinine (ng/ml)		
		Exposed	Non-exposed	Differences
Active smoking	M	319.2	0.85	318.3
	F	310.6	0.40	310.2
Spouse smoking	M	2.9	0.6	2.3
(among non-smokers)	F	1.0	0.3	0.7
Ratio of differences		Male 0.7%		
		Female 0.2%		

Table 4. Smoking related particulate levels in US smokers and non-smokers

Measure	Sex	Smoking related particulates (mg/day)		
		Active smoker	Non-smoker	Ratio
Inhaled dose	M	477.3	0.63	0.1%
	F	366.5	0.30	0.1%
Retention		80%	11%	
Retained dose	M	381.8	0.069	0.02%
	F	293.2	0.033	0.01%

and active smokers based on particulate matter would be more relevant. Table 4, based on Arundel et al. (1986), gives estimates for the US population of relative inhaled and retained particulate matter doses of non-smokers and active smokers. The ratios in Table 4 have to be adjusted upwards by a factor of 2 or 3 to make them comparable with the data in Tables 2 and 3, since (see Table 3) the difference between exposed and non-exposed non-smokers is two to three times the average level of non-smokers. This brings the inhaled dose estimates broadly in line with the cotinine estimates, though the retained dose estimates are about an order of magnitude lower. The lower figure for retained particulate matter is based on the work of Hiller et al. (1982a,b) who found that the collection efficiency of particles in environmental tobacco smoke is 11%, in contrast to the substantially higher figure of 80% for mainstream smoke. Robins (1986) also calculated that non-smokers take in the equivalent of an extremely small number of cigarettes per day in terms of respirable particulates. He noted that estimates of cigarette equivalents based on cotinine may be misleadingly high, since, whereas nicotine is in the particulate phase in mainstream smoke and will be absorbed mainly through the lungs, nicotine in ETS is mainly in the vapour phase, and, being water soluble, can be absorbed through the mucous membranes without ever reaching the lungs.

There appears to be a *huge discrepancy*, of two or perhaps three orders of magnitude between the claimed relative effects of passive and active smoke exposure and the much smaller relative exposure of passive and active smokers. What might explain this huge discrepancy?

One might argue that studies of active smoking, by including exposed and non-exposed non-smokers in their comparison group, underestimate the effect of active smoking so that the ratios in Table 2 are too high.

This is irrelevant for three reasons:

(a) the comparison between Tables 2 and 3 is in fact direct and not affected by this false baseline problem,
(b) failure to take the false baseline into account would have virtually no effect if risk was proportional to exposure and exposures in passive smokers are so low and
(c) it ignores a bias in the opposite direction due to failure to take into account the fact that smokers obviously have greater passive smoke exposure than do non-smokers.

Another point to be considered is duration of smoking. Since, in active smokers, risk of lung cancer is approximately related to the 4th power of duration of smoking (Doll and Peto 1978), one might infer that failure to take account of differences in duration might cause relative bias by a factor of 3.2 (= $60_4/45_4$) when comparing a 60 year old non-smoker exposed to passive smoke from birth and a 60 year smoker who started at age 15. Actually, the relative bias will be much less than this for two reasons. First, by no means all passive smokers will have been exposed since birth. Second, the "duration to a power" formula is only a valid approximation at smoker doses. Assuming a multistage model, it can easily be shown that at low doses the excess risk in relation to passive smoking becomes approximately linearly related to duration of smoking.

Neither of the above points really affect the huge discrepancy for which an explanation is being sought. If one is still wishing to accept the epidemiology as valid, one would have to seek an explanation either in a greater toxicity of ETS than mainstream smoke or in a greater susceptibility of non-smokers. While there is evidence that sidestream smoke has higher concentrations of some toxic chemicals than mainstream smoke, the relevance of this finding to environmental tobacco smoke which is aged, vastly diluted, chemically altered sidestream smoke, is not at all clear. There does not appear to be any direct evidence that ETS is particularly noxious. Nor is there any direct evidence that active smoking reduces susceptibility to relevant effects of ETS.

Limitations of Epidemiology

While it is not possible to completely rule out such explanations, the obvious alternative explanation – that the epidemiology is in some way biassed – seems on the face of it much more plausible. While the claimed effect of passive smoking may be large when viewed against the magnitude of effect predicted on dosimetric grounds, it is actually quite small when viewed against the magnitude of effect it has proved possible in the past to reliably identify using epidemiological methods. Alderson (1983) has suggested that a well designed case-control study should be able to confirm a two fold difference in risk but that, for differences less than this, the power of the study design may be inadequate. While case-control studies are particularly susceptible to a variety of sources of potential bias, this conclusion may well be true for any non-randomised epidemiological study (Lee 1988a).

In trying to assess whether bias might have arisen in the epidemiological evidence it is necessary to consider potential limitations of the available data. A number of general points can be made:

Unrepresentativeness

Although it is clear that the combined study population in Table 1 is not fully representative of non-smokers, this does not appear to be a serious issue, since studies have been carried out in the US, UK, Greece, Sweden, Japan and Hong Kong, and Wald et al. (1986) found no evidence of significant heterogeneity of relative risk estimates.

Sample Size

While none of the studies considered in Table 1 concern particularly large numbers of non-smokers with lung cancer, chance can hardly be the total explanation of the association between passive smoking and lung cancer since the overall relative risk estimate quoted by Wald et al. (1986) of 1.35 is quite highly statistically significant, with 95% confidence limits of 1.19-1.54.

Confounding

Not all the studies considered have taken into account the possible confounding effect of factors known or suspected to be related to lung cancer, such as occupation or nutrition. Although it would perhaps be expected that non-smokers married to smokers might to some extent share the tendency of smokers to work in dirtier jobs, standardisation for occupation, or indeed any confounding factor, has never been found in practice to explain any material part of the association between lung cancer and passive smoking. It does not seem likely that failure to take confounding factors into account has materially affected the issue.

Inappropriate Choice of Controls

General scientific principles demand that like should be compared with like as far as possible. In a number of studies, there were clear exceptions to this. One example is the study of Trichopoulos et al. (1981, 1984) in which controls came from a different hospital. This may cause bias if patients came from different catchment areas with different smoking characteristics. Another example is the recently reported study of Humble et al. (1987), in which virtually all the interviews with controls were conducted directly while much of the data for cases came from surrogates. While inappropriate choice of controls may have materially biassed a few studies, it does not seem very likely, however, that it is a major explanation for the huge discrepancy.

Inaccuracy of Disease Classification

It is well known that diagnosis of lung cancer is imperfect and studies such as those by Garfinkel et al. (1985) which took pains to check and review all available evidence are to be preferred to those that did not do so. However, random misclassification of diagnosis would be expected to reduce the observed association between lung cancer and passive smoking, not increase it, and differential misclassification of diagnosis does not seem very likely, inasmuch as the doctor making the diagnosis is likely to have been blind to the patient's ETS exposure in most cases, and not to have been affected by it even if he was, given most diagnoses were made before the first study on the issue was published in 1981.

Non-reporting Bias

A problem in combining results from various studies to come to an overall assessment of the evidence, by so-called "meta-analysis", is the possibility that the studies being combined are not representative of all those that have been carried out. In particular, overall estimates of relative risk may be biassed upward if a scientist is less likely to submit for publication, or a journal is less likely to publish, studies which show no significant relationship of disease to the factor of interest or a significant trend in the direction opposite to that expected in advance. Convincing evidence of bias resulting from this in the context of randomised controlled trials has recently been collected by Chalmers et al. (1987) and the problem may generally be greater in epidemiological studies. One can easily imagine an investigator running a range of statistical analyses, finding a few significant associations of interest, and then publishing papers on those, ignoring the non-significant relationships. One can also imagine journals not being too keen to given space to a paper on a new null association and one must inevitably wonder whether the reason the first two studies published on passive smoking and lung cancer (Hirayama 1981; Trichopoulos 1981) found a significant association was because first published papers on any association tend to be positive. Indeed, there seems a case for carrying out meta-analysis giving most weight to studies showing no association and least weight to studies published first.

Although it is obviously important to conduct research into the problems of non-reporting bias in epidemiological studies, it is difficult to claim that it is the full explanation of the overall association between passive smoking and lung cancer. The reasons for this view are two-fold. Firstly, the overall association remains significant (though the relative risk estimate reduces to 1.20), even after eliminating the Hirayama and Trichopoulos results. Secondly, the fact that lung cancer and passive smoking has been a very "hot" issue in recent years suggests researchers should now be able to publish results from studies showing no association between passive smoking and lung cancer risk.

Lack of Objective Measure of ETS Exposure

A limitation of all the published epidemiological evidence is lack of objective measurement of exposure to ETS. Subjects are classified mainly by whether or not they are married to a smoker and occasionally by reported degree of exposure outside the home, but there are no data available either on ambient levels of tobacco smoke constituents at home or at work or on levels in body fluids such as blood, urine or saliva. While (e.g. see Table 3) it can be shown that marriage to a smoker is indeed associated with increased levels of cotinine, the relatively crude method used for determining exposure leads to possibilities of bias in case-control studies where knowledge of disease may consciously or subconsciously affect reporting of ETS exposure. While this may have caused upward bias of the reported relative risk in some case-control studies, it can hardly explain the whole association, since it would not be expected to cause upward bias in prospective studies and the association seems as strong in prospective as in case-control studies.

Table 5. Hypothetical example of bias due to misclassification of 5% of smoking subjects as non-smokers

Smoking habit*		Assumed		Observed			
Subject	Spouse	N	Risk	N	Risk	Passive effect	Active effect
NS	NS	60	1	60 + 2 = 62	1.61	1	
NS	S	40	1	40 + 3 = 43	2.33	1.44	
NS	Total	100	1	100 + 5 = 105	1.90		1
S	NS	40	20	40 − 2 = 38	20		
S	S	60	20	60 − 3 = 57	20		
NS	Total	100	20	100 − 5 = 95	10		10.5

Assumed concordance = (60 × 60)/(40 × 40) = 2.25
Observed concordance = (62 × 57)/(43 × 38) = 2.16

* NS, non-smoker; S, smoker

Lack of Objective Measure of Active Smoking Status

Although considered last, this appears to be the most serious problem affecting the epidemiological evidence on passive smoking and lung cancer. As will be shown in the next section, completely erroneous conclusions can be reached when the "non-smokers" being studied actually include a small proportion of misclassified true smokers.

Misclassification of Active Smoking Habits as a Major Source of Bias

As shown in Table 5, misclassification of a small proportion of smokers as non-smokers, coupled with a tendency for smokers to be married to smokers ("concordance") can create an apparent positive effect of passive smoking when no actual effect exists. It also leads to an underestimation of the active smoking effect and of the concordance. The passive smoking bias depends critically on the assumed relative risk for active smoking, the degree of concordance and on the level of misclassification of subject smokers as non-smokers. This source of bias will also produce an artificial dose response relationship when the "non-smoking" subjects are divided according to the amount smoked by the spouse. It can be shown (Lee 1988b) that misclassification of non-smoking subjects as smokers and of smoking spouses as non-smokers causes a degree of bias that is minor compared with that resulting from misclassification of smoking subjects as non-smokers.

In an attempt to determine the extent to which smokers misreported their smoking habits and to which smokers tend to be married to smokers, Lee (1987) carried out three separate studies. In the first study, which concerned accuracy of reported current habits, 1775 British subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. They were then (with no prior warning) asked to provide saliva for cotinine analysis and 1537 agreed to do so. As shown in Table 3 there was in general a very marked difference between the cotinine levels of tobacco users and non-users. Using 30 ng/ml as a cut-off,

1.1% of self-reported non-users could be classified as occasional users, with levels of to 100 ng/ml, while 1.4% could be classified regular users, with levels above 100 ng/ml.

The second study, which aimed at obtaining information, on accuracy of past smoking habits, followed up in 1985 540 subjects previously interviewed in 1980 about their smoking habits. Ten % claiming on one occasion never to have smoked made inconsistent statements on the other occasion, with inconsistent smokers being more often men, old, smokers of fewer cigarettes and long term ex-smokers.

The third study, which aimed at obtaining information on smoking habit concordance, involved 8857 subjects aged 16+ interviewed regarding their own smoking habits and that of their spouse. The concordance ratio, 3.55 in men and 3.07 in women, was found to be rather greater than that assumed in the example in Table 5. Concordance rose with amount smoked. Thus, the chance of having a spouse who was a manufactured cigarette smoker was 22% for subjects who reported no such smoking, and 45%, 52% and 59% respectively for subjects who reported smoking 1-17, 18-22 and 23+ manufactured cigarettes per day.

From the data obtained, Lee (1987) concluded that misclassification could bias relative risk estimates in relation to passive smoking upwards by a factor of 1.31 in men and 1.24 in women, not significantly different from the pooled estimate of risk in relation to passive smoke exposure.

At about the same time as Lee presented his findings, Wald et al. (1986) used similar techniques to estimate the bias from misclassification, but based on a number of smaller, and less representative studies, not specifically designed for the purpose. They estimated this misclassification would have less effect, reducing the pooled estimate of risk only from 1.35 to 1.30, i.e. it had only caused upward bias by a factor of 1.04.

Examination of the detail of how the estimates of bias of Wald et al (1986) and of Lee (1987) were arrived at reveals three reasons for the difference. The first was that Wald et al. (1986) used an assumed relative risk of 8 for the effect of active smoking observed in women whereas Lee (1987) used 10. The second was that the calculations of bias by Wald et al. (1986) were mathematically inaccurate, due to confusion between true relative risks in relation to active smoking and those observed (which are affected by misclassification). These are less important than the third reason, which is that Lee et al. (1987) found that 1.4% (10/808) self-reported non-smokers were current regular smokers, whereas Wald et al. (1986) only found 0.14% (1/705) such cases.

In an attempt to reconcile this difference, I have recently conducted a detailed literature review of the evidence on misclassification of smoking habits, which will be published as a book early in 1988.

Despite the various study designs and populations involved a number of clear conclusions were reached:

(1) Even in circumstances that are apparently similar quite a wide variation in the extent of misclassification can be found.
(2) The proportion of "non-smokers" subsequently found actually to be smokers is markedly higher in smoking cessation studies than in studies where the respondent is under no special pressure not to smoke.
(3) The proportion of "non-smokers" subsequently found actually to be smokers is also markedly higher in lung cancer patients than in the general population. This is not surprising in view of the overall *a priori* expectation that a lung cancer patient actually is a smoker.
(4) Studies of "non-smokers" without lung cancer and under no special pressure not to smoke suggest that around 4% are likely actually to be current smokers. While not all

studies provide information on the extent to which such misclassified smokers smoke, and those that do indicate many of them are occasional smokers, it seems that 1 to 2% of self-reported non-smokers are regular smokers.

(5) In addition to these misclassified current smokers there are a somewhat larger number of ex-smokers misclassified as never smokers. Available information suggests that these tend to have smoked less and a longer time ago than average ex-smokers.

(6) None of the studies have investigated whether the extent to which smokers deny smoking depends on whether their spouse happens to smoke, which is of theoretical importance as it could materially affect estimates of bias.

(7) There is even now virtually no information on the extent to which smoking habits might be misclassified in Japan and Greece, from whence came the early epidemiological evidence on passive smoking and lung cancer. The only study in Japan, by Akiba et al. (1986), provided data suggestive of substantial misclassification of smoking habits. Here, of 187 men who reported not smoking in 1964–68, as many as 96 (51%) reported in 1982 that they had smoked.

While there is an obvious need for further research on misclassification of smoking habits the results of the review[1] suggested strongly that Wald et al. (1986) had seriously underestimated its importance.

Overall Conclusion

It has clearly been shown that there is a huge discrepancy between the relative doses of smoke constituents to which passive and active smokers are exposed and the much larger relative effect claimed from epidemiological evidence. The most likely explanation for this discrepancy seems to be a persistent bias affecting all the studies due to a small proportion of smokers being wrongly classified as non-smokers in the epidemiological studies.

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An Introduction to the Study of Smoking Using Urinary Hydroxyproline

H. Kasuga

Summary

The indicators used to identify the effects of environmental tobacco smoke (ETS) and exposure to low level nitrogen dioxide (NO_2) on the respiratory system are so weak that they can not be detected using traditional markers such as the increased prevalence of respiratory symptoms and a decrease in lung function. After studying urinary hydroxyproline (HOP) starting in 1977, we first reported the significant relationship between HOP and smoking, ETS and NO_2 in the air, in 1981. Since then, the coherent association between urinary HOP and the established pathological and biological development of lung diseases has been studied. Bias problems based on confounding factors, misclassification of nonsmokers and over- or underestimation of ETS effects also have been discussed.

Among articles presented by us during the past 4 years, several papers and some arguments for and against this study on urinary HOP were introduced:

1) The effect of cessation from smoking on the urinary excretion of hydroxyproline [19].
2) A prospective repeated cross-sectional study on the possible health effects caused by automobile exhaust and passive smoking [20].
3) Impact of smoking on the concentration and activity of alpha-1-antitripsin in serum, in relation to the urinary excretion of hydroxyproline. Matsuki H, Kasuga H et al., 1988.
4) Behavior of urinary hydroxyproline and effect of cigarette smoking in silicosis. Osaka F, Kasuga H, Matsuki H et al., 1985.
5) Opinions contrary to the relationship between urinary hydroxyproline and smoking, ETS and NO_2.

Introduction

Hydroxyproline (HOP) is one of the essential constituents in collagen and elastine and is an unique one which is not found in other tissues. Therefore, urinary HOP is regarded to be a potential candidate for the study of the breakdown of lung tissue due to smoking and environmental tobacco smoke (ETS).

As is generally known, the index symptom such as "a persistent cough and phlegm" based on the BMRC Questionnaire [1] is used frequently as a clinical marker, but it is not applicable for ETS effects because prevailing concentrations of ETS are estimated to be less than 1% of an undiluted mixture of sidestream and second-hand mainstream smoke. Therefore, urinary HOP as a biochemical marker for ETS effects appeared on the stage, and a causal relationship between smoking including ETS and its health effect was

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EPIDEMIOLOGY: ITS SCOPE AND LIMITATIONS FOR INDOOR AIR QUALITY

by KARL UBERLA

Prof. Dr. Med. Karl Uberla, born in 1935, studied medicine and psychology at the Universities of Heidelberg, Munich, Innsbruck and Freiburg. He got his M.D. in 1960 at Freiburg and his master's degree in psychology in 1962. From 1962 to 1963 he was visiting associate professor at the Department of Psychology at the University of Illinois. He worked as Research Assistant at the Institute fur Medizinische Statistik und Dokumentation of the University of Mainz. After his completing habilitation thesis in 1968 he got the chair as professor of medical statistics and data processing at Ulm. He served there as dean of the medical faculty and as vice president of the University. Since 1973 he has the chair of Medical Informatics, Biometry and Epidemiology at the University of Munich. During 1981-1985 he served as President of the Federal Health Office, Berlin. He has published more than 200 scientific articles on topics in Epidemiology, Biometry, Medical Data Processing, Risk Evaluation and Public Health.

Science is inherently controversial, particularly when it reaches its thresholds. Specifically, this is the case with low risk associations based on epidemiologic and toxicologic evidence. Examples of low risk associations in the control of indoor air quality are formaldehyde, asbestos, radon and "passive smoking". When SNOW in Great Britain analysed the association between cholera and water supply in the last century by epidemiologic methods, the relative risk was much larger. Today we are mainly concerned with low risk associations.

In my paper I will first address the scope of epidemiology and some of its basic limitations. In the second part I will deal with a case study of pas-

sive smoking. Does passive smoking cause lung cancer? What is the contribution of epidemiology to this question? Such a case study provides a fair idea of the problems in low risk estimation by epidemiologic and toxicologic methods.

Toxicology and epidemiology are partners in the assessment of risks. Toxicology ascertains whether a risk in man can exist. Epidemiology ascertains whether there is a risk in man and what the size of the risk is. The relation between toxicologic methods and epidemiologic methods is important. On what line of thought should we rely? From a scientific point of view toxicologic data can only show whether there can be a risk in man. Epidemiologic methods alone can show whether there really is such a risk in man and what the magnitude of such a risk is. The latter cannot be inferred from toxicology data.

1. THE SCOPE OF EPIDEMIOLOGY

There are some twenty definitions of epidemiology, which vary to some extent. I use here the definition by MACMAHON (1970): Epidemiology is the study of the distribution and determinants of disease frequency in man. This definition -like others- contains, on the one hand, the distribution of diseases and health in populations, the descriptive part of epidemiology. On the other hand, it contains the search for the causes and determinants of diseases, implemented by analytic epidemiology. Epidemiology has a rich history. It uses nowadays complicated statistical models. Descriptive and analytic methods both contribute to the evidence.

Epidemiology starts from available data. Widely used data are vital records and death certificates, morbidity surveys, data from disease notification and registration and dedicated studies. Basic characteristics of persons are used in epidemiologic studies. Such characteristics are age, sex, race and nationality, marital status, occupation and socioeconomic status. There are a host of other variables to be considered, but experience has shown that these are important for most studies.

Epidemiology studies the variation in time. Variation in time can hint at the factors underlying diseases. There are point epidemics, which are limited to space and time. There are secular changes and cyclic fluctuations and there exist sometimes clusters in time. Variations in place are very im-

portant to epidemiology. Differences in disease frequencies between countries can be partly attributed to socioeconomic and other differences between nations. International comparisons are therefore a useful instrument. Also the variation within a country can be an important source of our knowledge. The study of migrant populations -for instance the diseases of Japanese immigrants and their offsprings in the United States- offers an especially interesting source of epidemiologic evidence.

There are various study types in epidemiology. To make things simple I mention only two basic ones: cohort studies and case control studies. In cohort studies one starts in the present and observes into the future. In a defined group of people the exposure is assessed -for instance with environmental tobacco smoke (ETS)- and the lung cancer cases are observed in the following years. When performed properly such studies give good evidence. They need large numbers and are expensive. One can estimate incidences from such studies, one can estimate relative risks and one can also ascertain the attributable risk.

Case-control studies start with the cases and for every case one or several "controls" are selected. In both groups one tries to assess the exposure from history. This implies certain weaknesses. One can calculate a so-called odds ratio from such studies, which is an approximation of the relative risk in the case of low risk. One has to be careful in interpreting such studies for a variety of reasons. They are disturbed by bias, that is, systematic error. The memory is very susceptible to modifications of the reality. The controls might not be fair, confounders cannot be excluded and so on. However, case-control studies are not so expensive. One often has no other choice than to rely on the weaker evidence provided by such studies.

I want to mention three problems. Bias is a systematic error, which can occur in all epidemiologic studies. It is basically defined by the difference between the true value and its estimator. There are various sources and types of bias, for instance selection bias, interviewer bias and so on. Confounding means that the exposure-disease relationship is mixed up with the effects of extraneous variables. If such variables are observed, confounding can be controlled for, at least in principle. Misclassification means that a person is wrongly counted in a certain group, when he or she belongs to another group. A systematic trend in misclassification is called differential misclassification, which can give rise to wrong estimates of relative risk.

We use three different risk measures in epidemiology: incidence, rela-

tive risk and attributable risk. The incidence is the ratio of those getting a disease or experiencing an event during a certain time span in relation to those at risk. The relative risk is the ratio of two incidences: the incidence in those with a defined risk and the incidence in those without the risk. The relative risk is independent of the size of the incidence. So it does miss an important part of the information on the risk. Another risk measure is the attributable risk. It is a difference of incidences: the incidence of those under risk minus the incidence of those without risk. Basically this is the number of additional deaths which are caused by the exposure in a defined population. The attributable risk can only be used when one knows that there is a causal relation between exposure and event. Otherwise the attributable risk is a speculation. One must stress that these three risk measures should not be used separately. They are connected by definition and they should be viewed together since each of them contains only part of the information on risk.

A statistical association does not imply a causal relation. One has to keep this in mind. A statistically significant association is from the very beginning fictitious. It has often nothing to do with causal connection. We had for instance in our country during a certain time a statistically significant association between the number of nests of storks and the number of babies born, which clearly is an artifact. Causal influence is approached by exclusion of other explanations. There are well-known criteria which must be fulfilled in their majority, if one wants to infer a causal connection between exposure and effect from epidemiologic data. These criteria for a causal inference from epidemiologic studies were proposed by Bradford-Hill and have been modified. They are criticized nowadays by some epidemiologists. Only a few causal connections remain acceptable when one sticks to these criteria. They are very basic and can be relied upon. They surely are acceptable to scientifically oriented persons. However, they should not be used like a simple checklist:

- There should be consistency of association in the available studies.
- The results should be similar in the same circumstances and should be replicable.
- The strength and the intensity of an association is an indicator for causality. A causal connection is less probable with a low relative risk of 2 than with a high relative risk of 5 or 10.

- There should be specificity of association. Exposure, effect and way of action should be specific. This means that the exposure and the effect must be measured in a reliable and valid way.
- There should be a dose-response relationship. With higher doses there should be larger effects, at least in a certain dose range.
- The temporal relation between exposure and event should be such that the effect can be caused by the exposure. In cancer the latency period between exposure and event is 15 years and longer.
- Bias and confounding should be carefully excluded.
- There should be an impact of intervention. Removing the exposure should lead to a reduction of the risk, as was the case in the British doctors' study on the cessation of smoking and lung cancer.
- Finally, there should be biological plausibility.

Applying those criteria, one usually ends with limited or inadequate evidence. The International Agency of Research on Cancer (5) has used those criteria and proposed four levels of epidemiologic evidence in cancer research:

1. Sufficient evidence of carcinogenicity. There is a causal relationship between the exposure and human cancer.
2. Limited evidence of carcinogenicity. A causal interpretation is credible; however, alternative explanations (such as chance, bias and confounding) cannot be adequately excluded.
3. Inadequate evidence. There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
4. No evidence. Several adequate studies are available which do not show evidence of carcinogenicity.

Epidemiology as far as it is a science should adhere to stringent criteria. Otherwise it will become the playing ground for time-dependent opinions and prejudices. It is as honest to adhere to the null hypothesis as it is honest to accept the alternative hypothesis. In science the proof of the alternative hypothesis relies on those who propose it. In regulation one has to act before one knows exactly. This difference between knowledge and action is important. As scientists, we should not act before we know at least something.

2. SOME BASIC LIMITATIONS IN EPIDEMIOLOGY.

In epidemiology we are concerned with complicated questions. As in other sciences, there are serious limitations.

A first limitation is that adequate studies are usually not available. In most cases one ends up with very limited data with respect to the hypothesis in question. Epidemiologic studies, if properly conducted, take a long time. So data are missing and adequate evidence is not available.

Often the validity of the exposure and of the endpoint measures is low. Proxy variables are used, which might not correlate well with what we intend to measure.

Adequate studies need huge numbers and consequently are very costly. There are many important questions and only a very small part of them can be investigated. Epidemiologic research has to be centered on a few questions. In our time, the important questions are questions of low risk associations. The high risks -smoking, infections and so on- have been studied and can be studied easily when new problems arise. When the effect is small in comparison to chance, bias and confounding, we are in trouble.

In addition, there are conflicting group interests in all societies. Consequently, studies can be financed or not, can be interpreted in different ways and can be brought to the attention of the public and the legislative bodies or not. Scientists in epidemiology must stay independent, for instance from industry and from public pressure groups, sometimes even from governmental agencies. As scientists we have to rely on clear facts and not on opinion.

As in other sciences there are thresholds for human perception and knowledge in epidemiology. There are mainly two reasons for such thresholds: in order to recognize a small risk, one needs huge numbers. Random noise creeps in. We simply cannot observe one million people over 20 years without dropouts, losses and missing data. So the results are not reproducible. On the other hand we have to live in case-control studies with bias and confounding. Therefore, relative risks smaller than 2 are generally difficult to reproduce. They are then beyond the threshold of human perception and knowledge. Incidences smaller than 10^{-5} to 10^{-6} can usually not be reproduced in cohort studies. They are then beyond the threshold of human perception and knowledge.

There are also thresholds for human perception in toxicology. Inferring from animal to man is such a threshold. In toxicology we have the paradigm

of a missing threshold for carcinogenic substances. However, this paradigm is disputed more and more. A single molecule does not always meet its receptor and a single radiation quant does not always hit a target. So there must be cases in which there is an individual threshold. Furthermore there are repair mechanisms at nearly every level of carcinogenesis. For promotors the paradigm of a missing threshold has already been modified. In my opinion, the concept of a missing threshold for initiators will also disappear and will be replaced by more sophisticated models.

3. PASSIVE SMOKING AND LUNG CANCER: A SHORT CASE STUDY

There is no doubt that active smoking can cause lung cancer. Mainstream smoke contains a variety of carcinogens. A very high percentage, 90-95%, of lung cancer cases are smokers. A wealth of epidemiologic evidence shows a high risk increase with active smoking. There is hardly another single behavior which could be changed -like stopping smoking- which would have a comparable beneficial effect on the health and life expectancy of exposed populations. Stopping alcohol consumption could produce a beneficial effect of the same size order. Therefore, it is reasonable to try to reduce the exposure to carcinogens by active smoking, as it is reasonable to try to reduce the exposure to alcohol.

Lung cancer rates have been increasing in most countries since the beginning of the century when lung cancer was a very rare disease. The rates are much lower among women. During the last decades lung cancer has also increased among women. The most important risk factor for lung cancer is active smoking. Other risk factors are asbestos, radon, tuberculosis or genetic factors, but they are less important. DOLL and PETO estimate that about 90% of the lung cancer cases in men can be attributed to active smoking. Lung cancer leads to death in a very short time. One year after diagnosis only about 33 % still live, after five years only 10%. When lung cancer is diagnosed, the fatal destiny goes on.

There is very little known about the exposure of non-smokers to ETS. We looked at it in a representative sample in 1983 in Germany (7). Non-smoking men are exposed 1.20 hours a day in the working place, non-smoking women 0.40 hours. Considering only working non-smokers, men are

exposed 2.00 hours a day, women 1 hour per day, that is 8.3 and 4.3 percent of the total time. One has to consider that only 42% of the population are never-smokers in our country and that the real values are lower due to the method of data collection.

The question is whether passive smoking causes lung cancer. There are other unhealthy effects of passive smoking, like cardiovascular effects, bronchopulmonary effects in children and effects on the unborn child during pregnancy. I restrict myself to the case of passive smoking and lung cancer. The National Research Council (9) and the Surgeon General of the United States (10) have stated that there is or there might be a causal relationship. Also, the German Research Foundation followed this path, which is mainly based on reasoning by analogy.

The best available study is the study of HIRAYAMA (2,3,4). I will try to show how weak the evidence from this study is. The original data are given in Table 1.

TABLE 1: SMOKING HABIT OF HUSBAND BY AGE OF WIFE. ORIGINAL DATA.

WIVES	HUSBAND'S SMOKING HABITS			
	NON	1 - 19	20 +	TOTAL
40-49	4 7918	21 17492	21 12615	46 38025
50-59	14 7635	46 15640	31 8814	91 32089
60-69	16 6172	31 10381	10 3793	57 20344
70 +	3 172	1 671	2 292	6 1082
TOTAL	37 21895	99 44184	64 25.461	200 91540

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Married non-smoking women aged 40 and above -91,540 from a cohort of 265,118 adults in Japan- were asked whether they were smokers, and their husbands were also asked about their smoking habits. The women were followed for 15 years and their death certificates were collected. 200 women died of lung cancer. The table shows the numbers in the age groups according to the smoking habits of the husband. There are only six lung cancer cases in the highest age group, in which the majority of lung cancer cases occur in the population. From these numbers relative risks were calculated. The point estimate of the risk ratio in the group of the women married to men smoking more than twenty cigarettes per day was 1.56 to 1.79, depending on the way of standardization. There was a dose-response relationship which was also significant.

Why is this particular study not conclusive?

The study was not designed to test this hypothesis, but to screen for a wide variety of possible risk factors. It therefore cannot prove the hypothesis. The cohort was not representative of the population. There was an age selection bias. The indicator by which the exposure was measured -being married to a man who smokes- was neither reliable nor valid, nor specific. Also the endpoint was not assessed with validity. We know from experience that lung cancer diagnosis on the death certificate might be erroneous. Confounding factors were not adequately considered, for instance working place, air pollution or medical care. Bias in registering the fact that a woman was a non-smoker was neither controlled nor excluded. Differential misclassification is likely, since in 1965 smoking women were very rare in Japan. Almost nothing is known on the 200 cases. Case reports are missing; autopsy and histology are available in only 11.5%.

Each of these arguments alone could invalidate the results. HIRAYAMA at a recent conference refused to give his material to other researchers for a re-analysis. The core of evidence in the HIRAYAMA study is that during 1965, 200 women in Japan told an interviewer on a single occasion that they were non-smokers, and their husbands said that they were smokers -which could have been different before and thereafter- and their death certificates subsequently contained the -perhaps erroneous- diagnosis of lung cancer. This information is not a convincing scientific data base. I published these and other arguments in 1987 (11).

TABLE 2: DIFERENCES IN AGE DISTRIBUTION

AGE	PERCENT FEMALE POPULATION	PERCENT HIRAYAMA COHORT
40 - 49	42	42
50 - 59	32	35
60 - 69	20	22
70 +	6 *	1
	100	100

* In the female population 1965 in Japan over 40 there are 12 percent over 70 years old. We assumed here half ot them were still married with a living husband.

Recently we re-analysed the HIRAYAMA data (1) as far as they were published. Table 2 shows the differences in the age distribution between the female population in Japan in 1965 and the HIRAYAMA cohort. Only 1% in the cohort are older than 70 years in comparison to 12% in the population. We reduced this 12% to half -6%- assuming half the women were still married to a living man. It is obvious that there is a strong selection bias by age. When one removes this selection bias -I cannot go into details of calculation here- the relative risks become smaller and are no longer significant.

The first line of Table 3 shows the relative risk as calculated by HIRAYAMA, standardized by age of women only. In the 20+ group it is 1.56 and just significant at the one-tailed 5% level. Correcting for age selection bias the relative risks are much smaller and no longer significant. Considering subgroups -for instance women married to farmers and industry workers- only in the group of industry workers a high relative risk is present

TABLE 3: RELATIVE RISK IN THE HIRAYAMA STUDY

HUSBANDS SMOKING HABITS

	NON	1-19	20 +
RR HIRAYAMA*	**1.00**	**1.37**	**1.56**
IL_{90}		1.00	1.11
RR CORRECTED**	**1.00**	**1.03**	**1.29**
IL_{90}		.77	.94

* Standardized by age of women only
** Age selection bias removed, standardized by age of women
The corrected relative risks are small and no longer significant

after removing the age selection bias. This can be explained by the fact that women married to industry workers might be exposed also to other risks. If one leaves the women married to industry workers out, the relative risk is no longer different from unity. It also decreases considerably by assuming moderate numbers being differentially misclassified. I think this shows that the relative risk of non-smoking women married to men who smoke is not significantly different from unity, provided one considers age selection bias and misclassification. We have published this (1), but other epidemiologists do not share our view.

Another large prospective study from GARFINKEL in the US could not show a risk increase. I carefully evaluated the available studies last year

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and published the evidence with a critical view (11). I cannot describe the 10 case-control studies here in detail. They all have much weaker evidence compared to the HIRAYAMA study.

Nowadays, so-called meta-analysis are used to summarize the evidence from various studies in a formal way. This is useful when studies are similar, especially with controlled clinical trials. However, false plus false does not equal right. Meta-analysis are only valid when the studies included have some minimal quality. The discussion on meta-analysis in this field was started by a paper by WALD et al. (12) two years ago, in which 12 studies are summarized to a significant relative risk of 1.35. The report of the National Research Council and of the Surgeon General in the US followed this publication, the authors being partly the same. Also, the German Research Foundation could not refrain from adding incomparable studies to a single point estimate of risk.

We did our own meta-analysis of the same studies (8). As you can see from Table 4 we grouped the studies according to quality - whether histology was present, whether the exposure measure was somehow critically judged - and we gave a grade from 2 - 6 for overall methodological quality to every study. The study of TRICHOPOULOS got a grade 6 -the worst rating-, the study of GARFINKEL a 2 -our best rating. In the last column we decided for case control studies, whether a single study was of quality+ or of quality- according to these criteria.

In table 5 you see some of our results. The HIRAYAMA study was included with the relative risk corrected for age selection bias. We included women only, since men inflate only the denominator. We also left out the previous smokers in the studies of TRICHOPOULOS and KOO. All resulting relative risks are not different from unity, with the exception when one considers only the 4 case control studies of lower quality. Considering all 12 studies, the relative risk is 1.12. Leaving TRICHOPOULOS out gives 1.08. This study is a textbook example of how a case-control study should not be conducted and analysed. Introducing some cautious assumptions on misclassification, the numbers are still smaller. Also LEE (6) has remarked in his papers that at least part of the evidence can easily be explained by differential misclassification. One can look at the possible meta-analysis in a different way. With 10 case-control studies there are 1023 possible combinations

TABLE 4: QUALITY RATING OF STUDIES SELECTED FOR META-ANALYSIS

Author	Histology	Exposure	Quality Rating*	Resulting Group
HIRAYAMA	–	–	3	Cohort
GARFINKEL	–	–	2	Cohort
CHAN et al.	+	+	4	CC Quality +
CORREA et al.	–	–	5	CC Quality –
TRICHOPOULOS et al.	–	–	6	CC Quality –
BUFFLER et al.	+	–	4	CC Quality +
KABAT et al.	+	+	4	CC Quality +
GARFINKEL et al.	+	+	4	CC Quality +
AKIBA et al.	–	–	5	CC Quality –
LEE et al.	–	+	5	CC Quality –
KOO et al.	+	+	4	CC Quality +
PERSHAGEN et al.	+	+	4	CC Quality +

* 2 = acceptable, 3 = possibly flawed, 4 = bias and confounding suspected, 5 = major bias and confounding suspected, 6 = unacceptable.

The included studies are the same as in the paper by WALD et al. (1986) and by LETZEL and UBERLA (1988). We included women only.

for meta-analysis. Only 24 of them -2.3%- are technically significant. They are dominated by three studies of low quality, mainly by the TRICHOPOULOS study. All this shows that meta-analysis are very sensitive to the included data, that such sensitivity analysis give some insight into the combination of studies and that they presently do not contribute to our overall evidence regarding passive smoking and lung cancer.

Whether passive smoking causes lung cancer is an open question today. It is therefore not scientifically sound to calculate the attributable risk, i.e. the possible number of deaths attributed to passive smoking per year. All serious scientists refrain from such calculations. Of course, it cannot be ex-

TABLE 5: SUMMARY OF META - ANALYSIS

HIRAYAMA STUDY CORRECTED FOR AGE SELECTION BIAS CAUTIOUS ASSUMPTIONS FOR MISCLASSIFICATION		
	ORIGINAL DATA	MISCLASSIFICATION ASSUMPTIONS
	RR	RR
ALL 12 STUDIES	1.12	1.04
11 STUDIES (WITHOUT TRICHOPOULOS)	1.08	.99
2 COHORT STUDIES AND 6 CASE CONTROL STUDIES QUALITY +	1.04	.97
6 CASE CONTROL STUDIES QUALITY +	1.07	.90
4 CASE CONTROL STUDIES QUALITY	1.67	1.43

All relative risks are not significant with the exception of meta-analysis for 4 case control studies of quality —

cluded that there is a causal relationship. If there is an effect, it is likely to be very small compared to other risks.

The majority of criteria for a causal connection are not fullfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not

adequately excluded, there is no intervention study, significance is only present under special conditions and the biologic plausibility can be judged controversially.

There is room for honest differences in opinion. The jury is still out. All epidemiologic evidence can be explained by bias, confounding, misclassification and chance, nearly in the same way as by accepting the alternative hypothesis. Overall, according to the levels of the IARC, there is only inadequate evidence.

Whether passive smoking causes lung cancer is a serious hypothesis. The majority of publications in the field is a little in favor of this hypothesis. However, as I have said, I personally prefer to stay with the null hypothesis for the time being, following my careful analysis of the available evidence.

What can we learn from such a case study in low risk association? Toxicological studies alone cannot provide evidence on the size of a risk to man from indoor air pollution. There is not a single animal study with ETS which succeeded in producing lung cancer. Epidemiologic studies are the way to ascertain whether there is a risk in man, and what the size of the risk is. There are thresholds for human perception and knowledge in epidemiology: relative risks smaller than 2 and incidences smaller than 10^{-5} to 10^{-6} are such thresholds. The concept of a missing threshold for carcinogens should be replaced by more sophisticated models, when one tries to assess the cancer risk of indoor air quality.

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Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data

K. Überla and W. Ahlborn

The statistical association between environmental tobacco smoke and lung cancer is controversial. The Hirayama Study seems to provide sound epidemiological evidence supporting this hypothesis. In a recent paper [6] I have analyzed the published studies. Regarding the Hirayama study the following facts have to be kept in mind:

- The study was not designed to test the hypothesis, whether passive smoking is associated with lung cancer or not. It can therefore only generate this hypothesis, not prove it.
- The cohort was not representative for the population of Japan. A selection bias is possible.
- The exposure indicator – the fact of being married to a man who smokes – is not reliable, not valid and not specific.
- The event indicator – dying on lung cancer as noted on death certificates – is neither reliable nor valid.
- Various confounding factors – for instance exposure at the working place, indoor air pollution, overall air pollution, type of medical care – were not accounted for.
- Bias in registering the fact, that a woman is a nonsmoker, was not controlled. Resulting differential misclassifications of the cases, who were smokers and had to be excluded, have not been considered.
- Almost nothing is known about the 200 cases. No case reports are available, autopsy and histology are available in only 11.5%.

The core of the information, on which the results of this study rely, is

1) that during 1965 200 women in Japan told an interviewer on a single occasion that they were – during that time – nonsmokers and their husbands told that they were smokers, which might have been different before and afterwards and
2) that their death certificates subsequently contained the diagnosis lung cancer, which might have been erroneous.

Such sparse information does not seem to be convincing.

In our paper we consider three questions:

1) What is the relative risk when one removes the selection bias regarding age of women in the Hirayama cohort?
2) What is the relative risk for women married to men with different occupations, when one removes the selection bias regarding age of men?
3) What is the relative risk when additionally some differential misclassification is assumed?

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Material and Methods

We start from Tables 1, 2, and 3 of Hirayama 1984 [4]. These tables contain the most detailed published data. In order to check our program, we reproduced some of the reported relative risk estimates with good accuracy.

There are marked differences between the Hirayama cohort and the female age distribution over 40 in the population of Japan 1965. Women 50–59 are overrepresented, women older than 70 are severely underrepresented. In this age group only a single case from 12 was observed. The investigated cohort certainly has a severe selection bias by age, which needs no statistical test. This is likely due to the fact, that the smoking behaviour was not known in the elderly or that the husbands of older women have died. Since it takes 20 years and more from exposure to lung cancer, older women surely are relevant and should not be excluded. The majority of lung cancer cases occur in older age groups, in Germany more than 67% in women over 65 years.

In order to answer the question what the relative risk is when the age selection bias is removed, we adjusted the data to the age distribution of the female population of Japan.

Table 1. Differences between Hirayama cohort and the female age distribution over 40 in the population of Japan 1965*

Age group	Percent female	
	Japan population	Hirayama cohort
40–49	39	42
50–59	30	35 ↑
60–69	19	22
70 +	*12*	*1* ↓
	100	100

* Population Census 1965. Statistical survey of economy of Japan; 1967. Ministry of Foreign Affairs of Japan.

Table 2. Smoking habit of husband by age of wife.* Original data

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	4	7,918	21	17,492	21	12,615	46	38,025
50–59	14	7,635	46	15,640	31	8,814	91	32,089
60–69	16	6,170	31	10,381	10	3,793	57	20,344
70 ±	3	172	1	671	2	239	6	1,082
Total	37	*21,895*	99	*44,184*	64	*25,461*	200	*91,540*

* Table 2 of Hirayama 1984.

Table 3. Smoking habit of husband by age of wife*. Removed selection bias: Data adjusted to the age distribution of women in the population

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	3.91	7,748.8	19.12	15,927.8	20.02	12,024.0	43.05	35,700.6
50–59	12.49	6,813.7	38.20	12,987.1	26.95	7,661.2	77.64	27,462.0
60–69	14.25	5,496.6	25.70	8,604.9	8.68	3,291.1	48.63	17,392.6
70 +	32.02	1,835.9	9.93	6,664.2	20.79	2,484.7	62.74	10,984.8
Total	62.67	*21,895*	92.95	*44,184*	76.44	*25,461*	232.06	*91,540*

* Table 2 of Hirayama 1984.

The technique of iterative proportional fitting of a contingency table to given marginals as described by Bishop et al. [1] or by Hartung et al. [3] was used. This technique keeps the risks constant as observed in every cell and changes the marginals and the cell counts according to the given age distribution of the population. Iterative proportional fitting of contingency tables to given marginals is a well known technique in multivariate statistics and can be applied here without changing the observed interrelations between smoking habit, occupation, and lung cancer. From the fitted or adjusted tables the risk ratios are calculated in the usual way. Such risk ratios based on data with removed age selection bias are the correct ones and should be used.

One has to require that there should be no selection bias by age and the cases should be included as they would have occured in the population. Otherwise statistical tests and p-values are not very meaningful.

Table 2 shows the original data by age of wife. The cells contain the number of lung cancer cases and those under risk as published by Hirayama. The 1–19 group includes ex-smokers in this and the following tables. 200 cases out of 91,540 women were observed. Iterative proportional fitting to the female age distribution of the population leaves the hatched numbers constant. The others are adjusted using a right hand marginal which is made proportional to the age distribution of the population.

Results

Table 3 gives the results of iterative proportional fitting to the female age distribution of the population. It contains the numbers of those under risk and of lung cancer deaths as they would have been observed, if Hirayama had not excluded or preferred certain age groups. The age selection bias is removed. The risks in the individual cells are still the same as those observed by Hirayama. Also the structure of the common distribution regarding age, smoking habit and lung cancer is unchanged. Hirayama would have totally observed 232 cases instead of 200, with the corresponding numbers in the individual cells, had he included all women as they live in the population. This table is the best available starting point for age-standardized risk ratio calculations. It was not used so far.

Table 4. Relative risk by age of women*

	Husbands smoking habit		
	Non	1–19	20+
$\widehat{RR}$	1.00	*1.37*	*1.56*
IL_{90}		1.00	1.11
MH-CHI		1.51	2.27
$P_{one\ tailed}$		0.065	0.012**
$\widehat{RR}$	1.00	*0.77*	*1.06*
IL_{90}		0.59	0.80
MH-CHI		2.19	0.27
$P_{one\ tailed}$		0.014***	0.395

Upper part: standardized by age of women only.
Lower part: age selection bias removed and standardized by age of women.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 2 of Hirayama 1984.
** "Significant" in positive direction.
*** "Significant" in negative direction.

In the upper part of Table 4 you find the risk ratios standardized by age only, as done by Hirayama. The lower part are the risk ratios after removing the age selection bias. In the upper part the weighted point estimate of the rate ratio is 1.56 in the 20+-group and is technically "significant". IL_{90} designates the lower point of the 90-percent confidence interval in this and the following tables, as it was used by Hirayama.

This risk increase disappears completely when one removes the selection bias by age. In the 20+-group the rate ratio is 1.06, hardly a relevant risk increase. In the group of 1–19 cigarettes per day it is 0.77 which is a technically significant risk decrease. The adjusted rate ratio, considering all those exposed in one group versus those not exposed is 0.901 with a confidence interval including unity. If Hirayama had observed the cases as they occur in the female population without selection bias by age, he would have observed no risk increase, but a risk decrease. This is the main result of our reanalysis, which corresponds well with the result of the prospective American cohort study as published by Garfinkel [2].

We now consider two occupations, farmers and industry workers. From the upper part of Table 5 one can see that the relative risk for wives of farmers seems substantial, when one standardizes by age of men only. The point estimates of the rate ratios are 1.48 and 1.63 respectively. This was observed earlier and had no adequate explanation. If one removes the selection bias by age and adjusts to the male age distribution of Japan – the numbers in the lower part of Table 5 – the rate ratios are 0.85 and 0.82, not different from unity. This seems more plausible.

Considering the wives of industry workers only, in the upper part of Table 6, the point estimates of the rate ratios are 1.77 and 2.27, standardized by age of men, being not significant. Removing the age selection bias – in the lower part of Table 6 – there is a remarkable risk increase to 4.60 and 6.90, which is significant. However, there are only

Table 5. Relative risk: wives of farmers only*

	Husbands smoking habit		
	Non	1–19	20+
$\widehat{RR}$	1.00	*1.48*	*1.63*
IL_{90}		0.97	1.01
MH-CHI		1.48	1.92
$P_{one\ tailed}$		0.069	0.027
$\widehat{RR}$	1.00	*0.85*	*0.82*
IL_{90}		0.59	0.53
MH-CHI		0.42	0.53
$P_{one\ tailed}$		0.337	0.296

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

Table 6. Relative risk: wives of industry workers only*

	Husbands smoking habit		
	Non	1–19	20+
$\widehat{RR}$	1.00	*1.77*	*2.27*
IL_{90}		0.70	0.84
MH-CHI		0.73	0.81
$P_{one\ tailed}$		0.232	0.208
$\widehat{RR}$	1.00	*4.60*	*6.90*
IL_{90}		1.71	2.45
MH-CHI		2.50	2.78
$P_{one\ tailed}$		0.006	0.003

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

9 lung cancer deaths in the 20+-group and only 3 in women 70 years and older, which are small numbers, but these are numbers observed and used by Hirayama and his risk structure is unchanged. Thus only in the subgroup of women married to industry workers there is a risk increase, in all other occupations there is no risk increase. Omitting industry

Table 7. Relative risk: assumed differential misclassifications*

Number of cases assumed misclassified and removed from exposed groups		Husbands smoking habit		
		Non	1–19	20 +
n = 10 = 5%	R̂R	1.00	*0.74*	*1.00*
	$P_{\text{one tailed}}$		0.006	0.469
n = 20 = 10%	R̂R	1.00	*0.70*	*0.93*
	$P_{\text{one tailed}}$		0.003	0.383
n = 30 = 15%	R̂R	1.00	*0.66*	*0.85*
	$P_{\text{one tailed}}$		0.001	0.238

Age selection bias removed and standardized by age of women.
R̂R: Weighted point estimate of rate ratio.
* Calculated from Table 2 of Hirayama 1984.

workers, the point estimates of the rate ratios are 0.90 and 0.89, not significantly different from unity. These findings are consistent with the assumption of confounding factors in women married to industry workers, who might be exposed to other environmental hazards. Our calculations show that by removing selection bias by age, one can explain hitherto implausible results.

Active smoking is correlated among married couples. In a society in which female smokers were very rare in 1965, more women married to smokers will declare themselves nonsmokers than the other way round. One has therefore to considerr biased or differential misclassification. There are likely more women with lung cancer, who have been misclassified as nonsmokers and have to be removed from the cohort, than the other way round.

We made some moderate assumptions regarding differential misclassification, as shown in Table 7. In order to examine how sensitive the relative risk is we removed 10, 20, and 30 cases from the exposed groups – corresponding to 5, 10, and 15 percent.

Assuming 30 misclassified cases – 15 percent, a percentage which has been observed in the literature [5] – the rate ratios are 0.66 and 0.85. In the group 1–19 cigarettes per day all the risk estimators are significantly smaller than unity. Our personal opinion is that 10 differential misclassified cases from 200, who have to be omitted, are a fair number. The corresponding weighted point estimates of the rate ratio are 0.74 and 1.00. These risk estimates are as reasonable as other risk estimates calculated from the Hirayama data. They indicate – if anything – a risk decrease, not a risk increase.

Discussion

Reanalyses of data, which have been collected by others are not easy. This is because information is not completely available, because information might be misinterpreted or because one has to take another view in order to come closer to the acceptable truth. Our calculations do not diminish the great value and impact the Hirayama study had on the epidemiology of passive smoking. They show however, that reasonable alternative views

Table 8. Reanalysis of Hirayama's data: summary of relative risk

		Husbands smoking habit		
		Non	1–19	20 +
Age selection bias removed and age-standardized (women)	R̂R	1.00	*0.77*	*1.06*
	$P_{\text{one tailed}}$		0.014	0.395
Without industry workers, age selection bias removed and age-standardized (men)	R̂R	1.00	*0.90*	*0.89*
	$P_{\text{one tailed}}$		0.394	0.179
10 cases assumed misclassified, age selection bias removed and age-standardized (women)	R̂R	1.00	*0.74*	*1.00*
	$P_{\text{one tailed}}$		0.006	0.469

R̂R: Weighted point estimate of rate ratio.

on the same data are possible, which lead to opposite conclusions. Our findings are in contrast to Hirayama's thesis that – based on his data – there is a substantial statistical association between passive smoking and lung cancer.

As long as there is no other independent and sound epidemiological evidence, it should be left to the individual scientist which analysis of the same data he thinks is more appropriate. We do not hold that our view is the only correct one. We do hold however, that the risk ratios calculated by us, removing age selection bias, are as valid as other risk estimates. To our opinion they are more appropriate, since they go back to the population and not to a selected sample. Even when one would take another marginal, for instance the age distribution of wives still married to living men – which was not available – the effect would be considerable. Our risk estimates are a consequence of the data published by Hirayama and cannot be rejected from the study data, as they are published so far.

To summarize (Table 8): Removing the age selection bias in the Hirayama study one gets a relative risk of 1.06 in the group of women married to men with more than 20 cigarettes per day. In the group of women married to men with 1–19 cigarettes per day the relative risk is 0.77, a technically "significant" risk decrease. If Hirayama could have observed the lung cancer cases as they occur in the female population, he would have observed no risk increase, but a risk decrease to around 0.90, considering those exposed versus those not exposed. This fact deserves attention.

If one omits the wives married to industry workers because of possible confounding factors in this group, the relative risk is 0.90 and 0.89 respectively. This is of the same size order and smaller than unity. Here we could adjust and standardize by occupation and age of men only, which is not as appropriate as by the age of women.

If one assumes that 10 cases are differentially misclassified and removes them from the exposed groups, the risk estimates are 0.74 and 1.00, respectively. Our findings demonstrate how sensitive the data of this study are and how weak the evidence for a statistical association between passive smoking and lung cancer might be. In view of these and other facts some of which we mentioned in the introduction, the null hypothesis might be true as well and seems to be consistent with the Hirayama data in the same way as the alternative hypothesis.

We would be glad to apply our technique to more detailed data if we can get them from Hirayama, for instance in order to adjust by occupation of men and age of women, or by occupation of men and by age of women married to a husband who is still alive. We are ready to modify our view if such data can support the alternative hypothesis better than the published data. We do hope, that our calculations give rise to a fruitful discussion. The methods we used here might be of interest to the analysis of other cohort and case control studies.

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What Is the Epidemiologic Evidence for a Passive Smoking-Lung Cancer Association?

N. Mantel

Summary

Two survey articles of reports on the association of passive smoking with lung cancer have recently appeared, and also a comprehensive report on the subject of environmental tobacco smoke by a committee of the National Research Council of the United States. The observed excess over a relative risk of unity cannot be explained by chance. Nor can it be fully accounted for by a particular source of bias, the false claims of being non-smokers by individuals who were active or ex-smokers. That possible source of bias leads, in one summary survey, to reducing a relative risk of 1.35 to 1.30, but from 1.34 to 1.15 in the National Research Council report. The latter report suggests that statistical significance would no longer obtain, perhaps, particularly, because of other possible biases. However, to get an estimate of the correct relative risk due to passive smoking, allowance has to be made for actual exposure to passive smoking of those not exposed at home. Thus, the 1.30 is adjusted upwards, by 18 in one survey, to 1.53, but by only 8% in the National Research Council report to 1.24. The National Research Council report had given an anticipated relative risk of 1.1 based on dosimetric considerations. But it is suggested here that that could be as low as 1.05, too low to be detected in an epidemiologic investigation – in any case it would be based on hypothetical assumptions.

In November of 1986 there were two near-simultaneous review articles addressing the subject of passive smoking and lung cancer. One was an invited guest editorial by Blot and Fraumeni in the Journal of the National Cancer Institute, the other a contemporary theme discussion by Wald et al. in the British Medical Journal [1, 2].

There was substantial overlapping in the two articles of the various publications on the subject, and on the basis of which the conclusion of a significant positive association was made. The article by Wald et al. gave, perhaps, more statistical detail about the results of the several studies covered. But, to my mind, there was uncritical acceptance of the results of all the studies. Blot and Fraumeni did suggest that there were some flaws in a particular study, that by Hirayama [3], but decided that any inherent biases in that investigation could not have given rise to the observed elevated risk.

From their overall evaluation of 10 case-control studies (all 10 gave results for females, five separately for males as well) and three prospective studies (two of these covered males separately), which provided 20 separate relative risk (actually odds ratio) values, Wald et al. came up with a summary relative risk of lung cancer due to passive smoking of 1.35 (95% limits 1.19 to 1.54). They trim this down to 1.30 on the basis that some of the presumed non-smokers exposed to passive smoking were actually smokers. Then, on the added basis that even those unexposed to passive smoking at home may still have been exposed when away from home, they raise their estimate of relative risk to 1.53. But note that this last modification presupposes the answer, that passive smoking does

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Anyway, let's have a look at some of the summary data given. Collectively, for wives of non-smokers we have 32 lung cancers among 21 895 women versus 86/44 184 for ex-smokers or light smokers versus 56/25 461 for heavy smokers. That would yield a single df χ^2 by the method Dr Hirayama apparently used of 3·31, or a χ value of 1·82, not significant, two tailed, at the 5% level. Dr Hirayama, however, reports a χ value of 3·30, with a two-tailed probability level beyond 0·1%. The question then is whether he has conducted a more refined analysis, about which he is giving us no clues, or he has mistakenly interpreted his χ^2 value as a χ value.

As an example of a particularly striking association, Dr Hirayama concentrates on the results for non-smoking wives of agricultural workers aged 40-59. The corresponding data for this group are 3/5 999 versus 20/12 753 versus 16/7 150, which would yield a χ^2 of 6·45, a χ value of 2·54. Dr Hirayama reports a surprisingly close χ value of 2·60, with an associated significance level of 0·94%. As an extreme outcome of several possible analyses available to him this is not really all that significant. But if the difference between 2·54 and 2·60 reflects only rounding errors in calculations rather than distinctly different analyses, this would make it more likely that Dr Hirayama's 3·30 value is a χ^2 rather than a χ, which, as such, does not have the extreme statistical significance which he has attached to it.

Much more careful analysis of the data would be needed before it can be claimed that a passive effect of smoking has been clearly established.

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To Dr Takeshi Hirayama

In a recent press release the Tobacco Institute in the United States challenged the statistical validity of your finding that non-smoking wives of heavy smokers have a higher risk of lung cancer. The central point raised by the Tobacco Institute was that you erred fatally in your calculation of a critical test statistic and therefore that your claim of a high level of statistical significance is wrong. The Tobacco Institute's assertions relied heavily on a speculation contained in a memorandum on your study by Dr Nathan Mantel. The purpose of this letter is to inform you of the details of Dr Mantel's analysis, and in particular the origin of the alleged arithmetical error. Your results, at least those published, do indeed display a high level of statistical significance. If there is an error of inference in your study, it is far less superficial than the alleged arithmetical mistake publicised by the Tobacco Institute.

The essential data are given in the attached table, which we derived from tables I and II of your paper in the *BMJ* (17 January, p 183). The population of non-smoking wives at the beginning of the prospective study and the number of lung cancer deaths during 14 years of observation are broken down according to the age, occupation, and smoking habits of their husbands. Also provided are the corresponding 14-year lung cancer death rates for each cell. At the bottom of the table the data for all age and occupational categories of husbands are combined.

In his memorandum to the Tobacco Institute, Dr Mantel calculated a χ^2 test statistic with one degree of freedom from the *combined* data, and obtained the result $\chi^2 = 3·31$, which would yield a two-sided $p = 0·07$. In performing this test he used the scoring 0, 1, 2 for the three smoking categories. This value of χ^2 looked suspiciously close to the value of $\chi = 3·299$ reported on page 183 of your paper. On this basis, Dr Mantel *speculated* that you may have failed to take a simple square root in your calculation.

If, however, a χ^2 test statistic with one degree of freedom is calculated from the *disaggregated* data in the table, then the result is $\chi^2 = 8·09$, which yields a highly significant two-sided $p = 0·004$. In making this calculation we used formulas (2) through (4) on page 694 of Dr Mantel's original paper,[1] which shows how to combine χ^2 statistics from the four independent contingency tables. The reason for the increase in statistical significance is that the dose-response relation between the husband's smoking habit and the non-smoking wife's lung cancer rate, which is apparent from the combined data, becomes even more prominent when the data are broken down by age and occupational categories of the husband. That is exactly what Dr Mantel's extension χ^2 was designed to test.

We reach the same conclusion of a high level of statistical significance when the disaggregated data are fitted to a number of plausible statistical models. For example, if P_{ij} denotes the 14-year lung cancer death rate of a non-smoking woman whose husband belongs to age-occupational category $i = 1, 2, 3, 4$ and smoking category $j = 1, 2, 3$, then the traditional relative risk model $P_{ij} = a_i \cdot r_j$ yields a good statistical fit with an equally strong level of significance. (The 6-degree-of-freedom χ^2 goodness-of-fit statistic is 5·3, with $p = 0·5$.) For this model, the estimated relative risk of lung cancer for the intermediate category of smoking husbands is 1·42 (95% confidence interval 0·95 to 2·13) by maximum-likelihood methods. The estimated relative risk of lung cancer for the heavy-smoking husbands is 1·87 (95% confidence interval 1·21 to 2·91). These estimates are consistent with the relative risks reported in your paper.

In fairness and respect to Dr Mantel, we wish to put out that his speculation of an arithmetical error was only a minor point in his memorandum. The greater part of Dr Mantel's criticisms was devoted to ambiguities in your method of presenting the results. Thus it is not entirely clear to us whether you based your statistical calculations on more finely disaggregated age and occupational groups than those reported in the paper and reproduced by us here. It is unclear whether you used the number of person-years at risk or the number of persons at risk in your calculations of statistical significance. It is also not clear to us whether you standardised on the ages of the wives themselves. Such calculations, if not already performed, would certainly make the analysis more conclusive. But we see no obvious reason why these additional analyses should produce substantially different results.

The Tobacco Institute's claim that your study is invalidated by a trivial arithmetical error has become an international news story. We recognise that you, as author of the paper under challenge, are in the most appropriate position to respond publicly. As your colleagues in the scientific community, we urge you to uphold the validity of your paper.

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[1] Mantel N, Haenszel M. *Journal of the American Statistical Association* 1963;58:610-27.

SIR,—The far-reaching implications of the paper on passive smoking (17 January, p 183) make it imperative to determine whether the data on which it is based are adequate for the purpose.

In none of his several reports on this population does Hirayama explain how he selected his study population. There are 46 prefectures in Japan. Within these prefectures there are 832 health stations. In the six prefectures from which the 69 health stations were selected there are 173 health stations. How were the 69 selected? In one report it was stated that they were the medically adequate ones, which would introduce certain biases. The six prefectures included in the study contain most of the heavy industries in Japan and also border the sea. Shipbuilding, for example, in which Japan leads in world production, is associated in the United States with asbestos exposure. Since shipbuilding is a major industry in one of the prefectures in the study, were the health stations selected for the study for residents in the shipbuilding areas? Industry in Japan supplies medical care to workers and their families as one of the perquisites of employment. Were the families covered by industry omitted from the study? If so, the healthiest segment of the population was omitted.

The figure of 91-99% of the population of the health stations is given to demonstrate the population basis of these data. To what population is Hirayama referring? Is the census in Japan taken of health stations—that is, of individuals eligible for care in health stations? Is not attendance at the health stations the option of the individual? In the *Japanese Almanac* for 1972, the proportion of females visiting the health stations ranges from 2·5% in Miyaga to 14·5% in Osaka. How can this be population based? And if it is population based why were the rates figured by the person-year method rather than on the actual population?

Personal interview surveys usually elicit more complete response than mailed questionnaires or hospital record searches. In this study, on the pivotal question of occupation 44 357 (31·04%)

*Lung cancer deaths in non-smoking Japanese wives during 14 years of observation: data based on tables I and II of Hirayama's paper**

Husband's smoking habit:	Non-smoker	Ex-smoker or 1-19 cigarettes day	≥20 cigarettes day
Disaggregated data			
Husband aged 40-59 years and working in agriculture:			
Population of wives at risk	5999	12 753	7150
No of deaths from lung cancer	3	20	16
Lung cancer deaths per 10 000	5·0	15·7	22·4
Husband aged 40-59 years and working elsewhere:			
Population of wives at risk	8021	17 923	13 434
No of deaths from lung cancer	8	20	20
Lung cancer deaths per 10 000	10·0	11·2	14·9
Husband aged 60 years or more and working in agriculture:			
Population of wives at risk	4407	7291	2241
No of deaths from lung cancer	14	32	8
Lung cancer deaths per 10 000	31·8	43·9	35·7
Husband aged 60 years or more and working elsewhere:			
Population of wives at risk	3468	6217	2636
No of deaths from lung cancer	7	14	12
Lung cancer deaths per 10 000	20·2	22·5	45·5
Combined data			
Husbands of all ages and occupations:			
Population of wives at risk	21 895	44 184	25 461
No of deaths from lung cancer	32	86	56
Lung cancer deaths per 10 000	14·6	19·5	22·0

* *BMJ* 1981;282:183-5.

women surveyed and 6245 (40·19%) of the women smokers were listed as unknown or not specified as to occupation. Was this study part of a larger study collected for a different purpose, a national health survey perhaps? This could explain this large number of unknowns in this important category.

It is unusual to have such a study based on the ages of the the husband at time of interview rather than on age of the study subjects, the wives. When the agricultural and non-agricultural comparisons were made, the experience of the wives of men over 69 was omitted, an important segment of the study population. Why was this? Clarification of these points would be appreciated.

A recent study in Japan by Minowa *et al*[1] considers the distribution of lung cancer mortality and many of the environmental factors in Japan. In this carefully conducted and explained study, the author states, "Smoking did not seem to explain the prefectural differences of lung cancer mortality." There was no significant difference between the prefectures with high and low consumption of tobacco. The high standardised mortality ratios were along the seacoast, in the highly polluted and heavy industry areas for both males and females. The areas in Hirayama's study were nearly all in the areas with the high standardised mortality ratios in the Minowa study. Aoki,[2] another reputable epidemiologist from Japan, reported in 1980 on the incidence of lung cancer and its mechanism as regards factors other than smoking. Before the second world war lung cancer was a rare disease but during 1947-60 the number of deaths increased rapidly. Such an increase cannot be explained by smoking. These authors make the point that Japan has a disproportionate amount of adenocarcinoma, and Hirayama also mentions the large number of adenocarcinomas in the cases from this study that had a postmortem examination. The proportion of adenocarcinomas of the lung in Japan, twice as high as in any of the developed countries in the world and validated by an outstanding Japanese thoracic specialist, Ishikawa,[3] indicates aetiological factors peculiar to Japan, specifically related to adenocarcinoma.

Since histology is critical in determining prognosis, treatment, and aetiology in lung cancer, and adenocarcinoma is a different disease from squamous-cell carcinoma, and is omitted from many studies on results of smoking because the relationship is not established, to attribute causal dependence to the single aetiological factor of passive exposure to tobacco smoke regardless of histology raises serious questions.

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[1] Minowa M, Shigematsu I, Nagai M, Fukutomi K. *Soc Sci Med* 1981;15D(1):225-31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541-50.
[3] Ishikawa S. *Jpn J Clin Oncol* 1973;3:19-30.

SIR,—The validity of the significance test used in my paper was kindly confirmed by prominent statisticians in many institutes, including the US National Cancer Institute and the Massachusetts Institute of Technology.

Professor Macdonald apparently misunderstood the method used in our study. A complete interview survey was done for 265 118 adults aged 40 and above at the time of (or in some cases just subsequent to) the national census in 1965 in 29 health centre districts in six prefectures. This was not a random survey but the satisfactory representativeness of the study samples with regard to demographic and social indices was confirmed after the survey. Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample. The husbands' ages are closely associated with wives' ages. Since smoking habit is a characteristic of the husbands, the husband's age was used. We have tables by wives' ages separately.

The age-occupation-specific mortality asked for by Mr Kornegay and Dr Kastenbaum is shown in the accompanying table I. The statistical test on the overall results revealed a highly significant association.

Garfinkel's results[1] in the United States, which failed to show a significant dose-response relationship between amount of cigarette smoking by the husbands and the mortality of their non-smoking wives from lung cancer, are not a surprise to me. The discrepancy could be partly due to different methodology. Our study in Japan is based on census population and husbands as well as wives were interviewed with a 95% response rate. Since Garfinkel's series was based on volunteers' interviews, the husband's smoking history was available only for 27·1% of the non-smoking wives with lung cancer, 153 out of 564, in sharp contrast to 72·3% in our series (174 out of 240).

When, however, one compares the three recent studies—those of Garfinkel,[1] Trichopoulos *et al*[2] and ours—the difference between the actual and the expected mortality from lung cancer in non-smoking wives of smoking husbands were all in the same direction (table II); and a sound researcher will conclude that the size of the study samples should be increased, especially in the US series.

Other possible reasons for the different results between the United States and Japan include (*a*) a higher percentage of office workers in females in the United States than in Japan, 31·9% and 14·6%, respectively in 1975; (*b*) a higher divorce rate in the United States than in Japan, 4·1% and 1·1%, in 1975 respectively, indicating the need for consideration of smoking habits of ex-husbands in the United States; (*c*) smaller room size in Japan; (*d*) absence of the custom of asking, "Do you mind if I smoke?" in Japan; (*e*) other confounding variables.

In the survey conducted in Aichi Prefecture, one of our study areas, the number of passively smoked cigarettes and the length of exposure in the household was measured to estimate the quantity of sidestream smoke inhaled by the wives (table III). The number of cigarettes passively

TABLE I—*Mortality for lung cancer in non-smoking women by age, occupation,* and smoking habit of the husband*

Husband's age	Husband's occupation	Husband's smoking habit: Non-smoker: No of deaths	Population	Ex-smoker or 1-19 cigarettes/day: No of deaths	Population	≥20 cigarettes/day: No of deaths	Population	χ	Two-tailed p values
40-49	Total	5	6229	12	15034	15	10764	1·367	0·17163
	1	0	324	0	653	0	566		
	2	0	90	0	231	1	293	0·932	0·35134
	3	1	908	1	2247	3	1867	0·650	0·51569
	4	1	476	0	993	0	1044	−1·646	0·09976
	5	1	2502	6	5941	9	3636	2·297	0·02162
	6	0	46	0	165	0	108		
	7	0	177	1	486	1	426	0·541	0·58851
	8	1	1112	3	3431	1	2241	−0·545	0·59575
	9	0	162	1	345	0	243	−0·148	0·88234
	10	1	432	0	542	0	340	−1·217	0·22360
50-59	Total	6	7791	28	15642	21	9820	2·164	0·03046
	1	0	345	0	593	2	446	1·740	0·08186
	2	0	175	0	253	1	319	1·020	0·30773
	3	1	817	4	1764	1	1324	−0·436	0·66284
	4	1	653	2	1133	4	1092	0·955	0·33958
	5	2	3497	14	6812	7	3514	1·455	0·14567
	6	0	35	0	89	0	50		
	7	0	120	0	273	1	234	1·120	0·26271
	8	2	1375	6	3478	2	2155	−0·502	0·61567
	9	0	164	0	378	1	251	1·243	0·21387
	10	0	610	2	869	2	435	1·611	0·10718
60-69	Total	16	7120	42	12443	19	4651	1·790	0·07345
	1	0	227	0	327	1	179	1·434	0·15157
	2	1	91	0	143	0	124	−1·413	0·15766
	3	0	305	2	594	2	327	1·341	0·17992
	4	2	508	5	822	1	500	−0·459	0·64623
	5	11	4084	31	6645	8	2152	0·918	0·35862
	6	0	9	0	31	0	14		
	7	0	45	0	82	0	55		
	8	0	805	3	1784	3	736	1·872	0·06121
	9	1	121	0	208	0	92	−1·311	0·18986
	10	1	925	1	1607	4	472	2·391	0·01680
70 and over	Total	5	755	4	1065	1	226	−0·694	0·48768
	1	0	32	0	30	0	5		
	2	0	21	0	14	0	4		
	3	0	18	1	36	0	8	0·255	0·79872
	4	0	48	0	73	0	20		
	5	3	323	1	646	0	89	−1·494	0·13518
	6	0	1	0	1	0	0		
	7	0	1	0	5	0	1		
	8	0	87	2	119	1	36	1·371	0·17038
	9	0	11	0	19	0	2		
	10	2	213	0	322	0	61	−1·672	0·09452
Standardised risk ratio for all groups		1·000		1·435		1·846		2·942	0·00326

*Occupation: 1—Professional and technical workers; 2—managers and officials; 3—clerical and related workers; 4—sales workers; 5—farmers, lumbermen, and fishermen; 6—workers in mining and quarrying occupations; 7—workers in transport and communicating occupations; 8—craftsmen, production process workers, and labourers; 9—service workers; 10—not classifiable and not reported.

TABLE II—*Observed and expected deaths from lung cancer in non-smoking women with smoking husbands*

	Observed	Expected	Difference	Ratio	χ^2	
Japan (Hirayama)	142	85·8	+56·2	+65·5%	36·81	Significant
USA (Garfinkel[1])	88	75·3	+12·7	+16·9%	2·14	Not significant
Greece (Trichopoulos *et al*[2])	29	12·1	+16·9	+139·7%	23·60	Significant
Total	259	173·2	+85·8	+49·5%	42·50	Significant

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clearly inadequate for the purposes at hand. Rather fine categorisation is used for husband's occupation, but analysis of the data does not indicate that this is a significant predictor. The stratification for age, on the other hand, is far too coarse. Variations of cancer incidence within 10-year age ranges are large compared with the variations attributed to the husband's smoking. Even relatively small differences in the age distribution of the three populations could thus produce the reported apparent effect. The use of husbands' rather than wives' ages for stratification compounds the problem.

The measure of risk is also inappropriate for a study of such extended duration. The number of person years at risk rather than the number of subjects should be used as the exposure variable, since many subjects would have died of other causes during the study. The appropriate procedure for analysing data of this type is given in Mantel's original paper.[1]

Finally, it is clear from the original paper that Dr Hirayama analysed several causes of death, but reported statistics only for lung cancer. The procedure of reporting only the most significant result from a choice of several possible dependent measures a posteriori is a common error which naturally leads to inflated estimates of significance. Only an appropriate multivariate test can properly estimate statistical significance in this situation.

The analysis reported must thus be regarded as inconclusive unless more refined analyses are able to confirm the results. We endorse the author's suggestion that further study based on larger samples is needed, but we emphasise that such studies can be useful only if the relevant biomedical data are recorded and analysed in sufficient detail to isolate the hypothesised effect from confounding factors.

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[1] Mantel N, Halperin M. *Journal of the American Statistical Association* 1963;58:611-27.

SIR,—Most of the questions raised in my letter (3 October, p 917) were not addressed in the response of Dr Hirayama that followed. The first readings of his original paper troubled me in view of his recognised work, so that before I commented I reviewed every Hirayama paper in the literature on this study population to see if the collective information might answer the questions. A map of Japan was constructed by prefectures and minor population subdivisions and the areas of the study were marked as nearly as they could be ascertained. Review of the reports on the epidemiology and clinical aspects of lung cancer of other Japanese scientists and finally a serious study of Japanese demography, industry, disease trends, and all pertinent data were made; so the questions asked were serious and responsible.

Dr Hirayama did not answer the question about how or why the specific health stations surveyed were selected, or how the few prefectures of the total in Japan from which the health stations were chosen were selected. He admitted that the selection was not random and states, "The satisfactory representativeness of the sample was confirmed after the survey." He does not say by what criteria this was confirmed.

Mapping of the areas selected for study and of the industrial concentrations shows them to be related in nearly every instance. Dr Hirayama states, "Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample." Asbestos and other industrial exposures would have to be considered according to the locations of the study areas and of the industrial complexes as revealed on the map of Japan. The areas were nearly all in the areas with high standardised mortality ratios in the excellent and fully documented countrywide epidemiological lung cancer mortality study of Minowa *et al*.[1] The tabulation on the basis of the husbands' ages is not explained. According to the median age at time of marriage in Japan, there is a difference between husbands' and wives' ages, the wives being generally younger. Dr Hirayama states, "We have tables by wives' ages separately." They were not found in the literature search on these data.

No response at all was made to the following questions: (1) Were the families whose medical care was covered by industry omitted from the study? (2) To what population is Hirayama referring? (3) Why were 31% of the women surveyed (and 40% of the women smokers) listed as unknown or not specified as to occupation? For a person to person survey, this suggests methodological problems. (4) Why were references to current Japanese studies by reputable men, Minowa *et al*[1] and Aoki,[2] whose findings did "not seem to explain the prefectural differences of lung cancer mortality" not mentioned? (5) The report by Ishikawa[3] on the preponderance of adenocarcinoma in Japan, in a footnote of which he acknowledges the assistance of Dr Hirayama, his colleague as a reviewer, is not referred to in the answer, although this is very important to this discussion.

Two new issues were introduced by Dr Hirayama in his response, one on the quantity of sidestream smoke inhaled by the wives, without any discussion of the quantity smoked in houses or in the presence of the wives. All the sidestream smoke of husbands' cigarettes would not be inhaled. A remarkably careful study on this subject was reported in 1978 by a French group that helps to explain the differences reported by different techniques of measurement. They improved and explained each innovation they used to overcome logistical problems noted in previous studies. They concluded, with valid proof, that on the strictly toxicological level there is no hazard for non-smokers. The report does not neglect to remark on the problems that are presented to a very important fraction of the population, however. The second issue introduced in the reply was that inhalation through the nose is different from the smoker's direct inhalation. This did not consider the superb filtering system, which would conceivably reduce the amount of ambient smoke inhaled by the wives.[4]

Finally, the far-reaching implications of this unproved passive smoking effect are already in evidence in the literature.

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[1] Minowa M, Shigematsu I, Nagai M, Fukutomi K. *Soc Sci Med* 1981;15D(1):225-31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541-50.
[3] Ishikawa S. *Jpn J Clin Oncol* 1973;3:19-30.
[4] Badre R, Guillerm R, Abran N, Bourdin M, Dumas C. *Annales Pharmaceutiques Françaises* 1978;36:443-52.

SIR,—Dr T Hirayama (17 January, p 183) reports a greater risk of lung cancer in non-smoking women when their husbands smoke than when they do not. Assessing the statistical significance of this association by a χ^2 trend statistic on one degree of freedom, Dr N Mantel (3 October, p 914) showed that a non-significant value of 3·31 is obtained if age and occupation are ignored. However, if these factors are taken into account, on the basis of data given in table I of Dr Hirayama's recent letter (3 October, p 916), a higher χ^2 value of 8·70 is obtained, which is statistically significant ($p<0·01$), and similar to, though not identical with, to the value of 10·88 given in his original paper. While this slight discrepancy might have been due, perhaps, to the use of narrower age bands in Dr Hirayama's original calculations, it is clear that the much more significant differences claimed in tables II and III of his letter are due to a statistical error.

Table II, which gives a very much higher χ^2 value of 36·81 for a similar comparison, is based on the false assumption that the lung cancer rate of non-smoking women with husbands who did not smoke is known precisely. The correct calculation, given in my table, gives a much lower level of significance for the Japanese data, and his calculations for the American[1] and Greek[2] data are similarly in error. Consideration only of women with smoking husbands has also led Dr Hirayama to conclude incorrectly that the American study was materially less powerful than the Japanese study because of sample size. In fact, the studies were of very similar power, a slightly smaller total number of deaths in the American study (153 compared with 174) being balanced by the greater stability of the denominator in the relative risk calculations, due to the greater number of deaths in women whose husbands did not smoke (65 compared with 32).

The source of the error in his table III is not clear, but the remarkably narrow 95% confidence bands for relative risk given in the table below the figure cannot be even approximately correct. How, for example, can the ratio of 2·94 given for the comparison of lung cancer rates between non-smoking men whose wives smoke (seven deaths out of 1010) and non-smoking men whose wives do not smoke (50 deaths out of 19 279) possibly have 95% limits as close together as 2·65 and 3·26—that is, $\pm 10\%$—when the 95% limits for the seven observed deaths are approximately 2 and 12—that is, $\pm 70\%$—and the variability of the relative risk must be greater than this?

Hugod, *et al*[3] have shown that under quite extreme passive smoke conditions, sufficient to produce a carbon monoxide air concentration of 20 parts per million, a non-smoker would take 11

Observed and expected deaths from lung cancer in non-smoking women in the Japanese study according to the smoking habit of their husbands

	Husbands do not smoke		Husbands smoke			
	Observed	Expected	Observed	Expected	χ^2	p
As given by Hirayama	32	(32·0)	142	85·8	36·81	$<0·00001$
Correct calculation	32	45·8*	142	128·2*	5·78	$<0·05$

* Standardised for age and occupation on the basis of data in table I of Dr Hirayama's letter (3 October, p 916).

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PASSIVE SMOKING

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Summary—Before 1980 the argument that passive smoking was a serious health hazard was rather tenuous. It was claimed that it produced allergic reactions, impaired driving ability, reduced exercise tolerance in patients with cardiorespiratory disease and increased the risk of bronchitis and pneumonia in first-year children. However, none of these claims provided convincing evidence relevant to the normal healthy adult nonsmoker. Many studies indicate that nonsmokers are unlikely to inhale more than a very small amount of those components of tobacco smoke traditionally considered harmful. It was surprising, therefore, when a study carried out in the USA showed reduced airways function and studies from Japan and Greece showed an increased lung cancer incidence in nonsmokers passively exposed to tobacco smoke in comparison with nonsmokers not so exposed. A review of the detail of these studies suggests that none provides conclusive evidence that passive smoking is seriously harmful, a view supported by a recent large study that was carried out in the USA and in which no significant relationship was found between passive smoking and lung cancer. More research is urgently needed, particularly to explore the influence of potentially confounding factors.

Introduction

Passive smoking is the inhalation of tobacco smoke other than by puffing on a cigarette, cigar or pipe. Study of it is relatively new, with few literature references before 1970. In this review a number of types of accusations that had been levelled against passive smoking up until 1979 are considered first. There follows a section summarizing the dosimetric aspects, understanding of which is fundamental to sensible evaluation of the epidemiological evidence, and then recent suggestions that passive smoking might be a more serious health hazard than hitherto considered likely are examined critically.

Early claims

Annoyance and irritation

That passive smoke exposure, especially under conditions of poor ventilation, can be annoying and irritating is a matter of common experience. By interviewing 250 nonallergic patients about their reaction to cigarette smoke, Speer (1968) found that 69% reported eye irritation, 32% headache, 29% nasal symptoms and 25% cough. Weber, Jermini & Grandjean (1976) found that the frequency of reported eye, nose and throat irritation increased with increasing concentrations of smoke in a sealed chamber and suggested that acrolein was the major offending substance. Subsequently, however, Hugod, Hawkins & Astrup (1978) showed that, although a gas-phase polluted atmosphere was as annoying as one polluted with whole sidestream smoke, air pollution with acrolein at three times the concentration present in sidestream smoke caused considerably less discomfort.

Allergy

The 1979 US Surgeon-General's Report (US Public Health Service, 1979) devoted a chapter to the subject of allergy and tobacco smoke. It concluded that the existence of such an allergy was not clearly established but that those with a history of allergies to other substances, especially those with rhinitis or asthma, were more likely to report the irritating effects of tobacco smoke. Whether this was a psychological, rather than a physiological, response is open to question.

Bronchitis and pneumonia in children

Colley (1974), who has been studying respiratory symptoms in children and young adults for many years, first reported evidence of a possible effect of parental smoking in 1974. In this study a slightly increased prevalence of cough in children aged 6–14 years whose parents smoked lost its significance when parental respiratory disease was taken into account. The author noted that "there was no suggestion that exposure to the cigarette smoke generated when parents smoked had any more than a small effect upon the child's respiratory symptoms".

Later in that year Colley, Holland & Corkhill (1974) published a follow-up paper showing that in children in the first year of life, but not in the second to fifth year, prevalence of cough was significantly higher in children of parents who smoked. This excess was still significant if the analysis was restricted to those parents who did not have phlegm. Despite noting that "the association could be a result of shared genetic susceptibility to respiratory disease between parents and children, to living in the same home environment, and to cross-infection within the family"

Abbreviations: CET = Cigarette equivalent time; COHb = Carboxyhaemoglobin; FEF (25–75%) = forced mid-expiratory flow; FEF (75–85%) = forced end-expiratory flow; FEV = forced expiratory volume in 1 second; FVC = forced vital capacity; NDMA = N-nitrosodimethylamine; PM = particulate matter.

they concluded that "a picture has thus emerged of a serious risk to infants in the first year of life from exposure to their parents' cigarette smoke".

A further study by Leeder, Corkhill, Irving *et al.* (1976) sustained these findings, demonstrating an increased prevalence of bronchitis, pneumonia and wheeze (but not asthma) in the first year of life in children whose parents smoked. More possible explanatory factors were studied than in 1974, including whether or not a sibling had symptoms, but standardizing for these did not affect the conclusions.

Whether passive smoke in the atmosphere of the home is the cause of these infections remains open to question. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) suggested that parental neglect may play a role. Also the fact that smokers are more sociable (Eysenck, 1965) could present more opportunity for the children to come into contact with infection.

Psychomotor effects

There has been some concern that relatively low levels of carbon monoxide may have an effect on psychomotor functions, especially in relation to driving a car. The literature reports a great discrepancy in the level at which blood carboxyhaemoglobin (COHb) may affect vigilance. Summarizing the literature, the 1979 US Surgeon-General's Report (US Public Health Service, 1979) concluded that effects seen at levels of COHb found in passive smoking conditions are measurable only at the threshold of stimuli perception and that effects of CO on driving performance and interactive effects of CO and alcohol are only found at higher COHb levels. A recent study by Guillerm, Radziszewski & Caille (1978), in which subjects drove a specially equipped car for 5 hours during the night, exposed either to air or CO sufficient to produce blood levels of 7 or 11% COHb, found no effect of even 11% COHb on driving precision or visual reaction time. This COHb level exceeds that achieved by all passive and indeed most active smokers.

Exercise tolerance

Aronow (1978) examined the effect of passive smoke exposure on 10 patients (two smokers, eight nonsmokers) with *angina pectoris*. Mean time of exercise until onset of angina in control conditions (COHb level 1·3%) was reduced by 22% after exposure to passive smoke in a ventilated room (COHb level 1·8%) and by 38% after exposure in an unventilated room (COHb level 2·3%). He also noted that the passively exposed patients had a raised heart rate and blood pressure. He attributed this to the possible absorption of nicotine, though he did not measure blood levels. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) considered it unlikely that the very low levels of nicotine absorption could be responsible for these physiological changes and suggested that the response could be due to stress following anxiety or aggravation induced by the smoke-filled room.

Summary of evidence available in 1979

Taking all this evidence together, it seemed clear that, while smoking was a source of annoyance to some, although not perhaps very annoying for many, the grounds for believing it to be a health hazard were rather thin. Where adverse effects were claimed they did not apply to the normal healthy adult nonsmoker and/or were not backed by particularly solid evidence. A statement made in a leading article in the *British Medical Journal* (1978) typified the generally accepted view at the time: "For the moment most—but not all—of the pressure for people (including many smokers) to have the right to breathe smoke-free air must be based on aesthetic considerations rather than on known serious risks to health".

Dosimetry

General

A number of totally misleading statements have been made about the dose received by a passive smoker. One example is that by Repace & Lowrey (1980) who, using a theoretical model combined with measurements of cigarette smoke particulate matter (PM) in various different environments, estimated that a nonsmoking office worker exposed to moderate passive smoke inhales the equivalent, in PM terms, of five cigarettes a day while a very heavily exposed nonsmoking musician working in a night club with a chain smoker for a room-mate inhales the equivalent of 27 cigarettes a day. Study of the detail of this paper revealed that the authors had used an extremely low yielding cigarette with a PM yield of only 0·55 mg/cigarette as a basis for calculating cigarettes per day. If, more realistically, a sales weighted average cigarette with a PM yield of 17·6 mg/cigarette had been used, the appropriate exposures would have become one-sixth of a cigarette per day for the officer worker and five-sixths of a cigarette per day for the musician. Even more outlandish was the recently reported claim of Lane quoted in the national press in the UK (*Daily Mail* and *Daily Telegraph* both of 2 June 1981) that "there is now medical evidence to show that the smoke breathed in by non-smokers is 18 times higher in tar and 12 times higher in nicotine than the smoke breathed by smokers...". The source of this claim undoubtedly comes from a table published by the Laboratory of the Government Chemist (1980), which showed that the ratio of sidestream to mainstream yields was 18 for tar and 12 for nicotine when a very low tar cigarette was smoked under machine conditions. Not only had the cigarette used as a basis for comparison a tar level some 10 to 15 times less than that normally smoked, but the fundamental error of confusing sidestream yields and ambient concentrations had also been made. The concentration of sidestream smoke is measured as it leaves the burning cone of tobacco between puffs, whereas what is relevant to the passive smoker is the concentration of smoke as it reaches him after dilution by room air. Ambient concentrations vary drastically depending on the degree of room ventilation but even under conditions of poor ventilation will be very considerably less than sidestream concentrations, which a nonsmoker would only receive if he were to keep his nose right on top of the cigarette.

A number of workers have measured the concentration of smoke constituents in ambient air and in body fluids. An important study by Hugod *et al.* (1978) measured air concentrations of a number of

Table 1. *Comparison of uptake of smoke constituents in smokers and passive smokers**

Smoke constituent	Mainstream yield inhaled by smoker (mg/cigarette)	Inhaled amount in passive smoking conditions (mg/hr)†	Cigarette equivalents/hr	Cigarette equivalent time (hr)
NO	0·30	0·182	0·61	1·6
CO	18·40	9·160	0·50	2·0
Aldehyde	0·81	0·214	0·26	3·8
Acrolein	0·09	0·013	0·14	7·1
TPM	25·30	2·300	0·09	11·1
Nicotine	2·10	0·041	0·02	50·0
Cyanide	0·25	0·005	0·02	50·0

TPM = Total particulate matter

*Data from Hugod, Hawkins & Astrup (1978).

†Volunteers were exposed in a closed, unventilated room to quite severe passive smoke conditions in which the air CO concentration was kept at 20 ppm over a 3-hr period.

constituents in a closed, unventilated room in which ten volunteers were exposed to quite severe passive smoke exposure conditions in which the air CO concentration was kept at 20 ppm. Comparing the estimated inhaled amounts of each constituent with those inhaled by a smoker they calculated cigarette equivalent times (CET) in hours for seven different constituents (Table 1). It can be seen that these estimates of the time taken to inhale the equivalent of one cigarette vary widely according to the particular constituent.

Nicotine

For nicotine, Hugod *et al.* (1978) estimated it would take a passive smoker 50 hr to take in as much as would a smoker smoking one cigarette, an amount they regarded as negligible. Their results are broadly consistent with those of Hinds & First (1975) who estimated that nicotine concentrations in various public places in the USA ranged from the equivalent of one-thousandth of a filter cigarette per hour in a bus station waiting room up to almost one-hundredth in a cocktail lounge. Similarly Russell & Feyerabend (1975) found that nonsmokers exposed experimentally in an almost intolerably smoky room, whilst having average urinary nicotine levels almost ten times higher than nonsmokers not deliberately exposed to smoke, had urinary nicotine levels 15 times lower than average smokers.

Total particulate matter

For total particulate matter, the constituent usually considered to be related to the excess of lung cancer risk in smokers, Hugod *et al.* (1978) concluded that the CET value is "so high that the passive smoker will never inhale more than what equals ½–1 cigarette per day"—a finding consistent with the conclusions of Repace & Lowrey (1980) if adjusted so that a sensible baseline cigarette is used for comparison.

Carbon monoxide

For CO, the conclusions of Hugod *et al.* (1978) are similar to those of Russell, Cole & Brown (1973) who, working with even more extreme conditions involving twice the exposure level for CO than that used by Hugod *et al.*, found half the CET value (i.e. 1 hour). Even despite this relatively low CET value, it is most unlikely that passive smokers will achieve blood COHb levels as high as 3%, which has been claimed to decrease the threshold for intermittent claudication and angina pectoris in patients with obliterating arterial disease (Anderson, Andelman, Strauch *et al.* 1973; Aronow, Stemmer & Isbell, 1974).

N-Nitrosodimethylamine

N-Nitrosodimethylamine (NDMA) merits mention in the context of passive smoking because of its unusually high ratio of sidestream to mainstream smoke deliveries (Brunnemann, Fink & Moser, 1980) and of its known biological activity.

Brunnemann, Adams, Ho & Hoffmann (1978) measured the levels of NDMA in the atmosphere for several indoor locations in the USA. The highest concentration found (0·24 ng/litre) was in a bar, and the authors calculated that a nonsmoker in this situation would inhale, in 1 hour, an amount of NDMA equivalent to that inhaled by a person actively smoking 17–35 filter cigarettes. Not only was this an extremely smoky atmosphere (their equivalent figure in a bank, where smoking was permitted, being one to two filter cigarettes), but the concentration considerably exceeded that (0·07 ng/litre) found by H. Altmann (personal communication, 1981), in a small (46 m^3) unventilated conference room in which 11 people smoked 64 cigarettes in 2 hours—conditions sufficient to produce nausea in the majority of those present. The significance of these low levels of NDMA is not clear. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) points out that the absorption of nitrosamine from environmental conditions is not necessarily equivalent to the absorption by smoking, while Brunnemann *et al.* (1980) have emphasized that "no epidemiological data exist linking human respiratory cancers to volatile nitrosamines".

Dosimetry—a conclusion

Hugod *et al.* (1978) concluded that "in spite of an often considerable subjective discomfort, exposing non-smokers to tobacco smoke under realistic conditions will not cause inhalation of such amounts of the components of tobacco smoke traditionally considered harmful, that a lasting, adverse health effect in otherwise healthy, grown-up individuals seems probable".

Table 2. *Vital capacities and expiratory flow rates in smokers and nonsmokers**

Sex	Group number	Smoking habits†	Percentage of predicted FVC	FEV$_1$	FEF 25–75%	FEF 75–85%
Male	1	Nonsmokers, no smoky environment	102	103	104	120
	2	Nonsmokers, smoky environment	99	98	91	95
	3	Smokers not inhaling	96	99	92	87
	4	Smokers: 1–10 cigarettes/day	95	97	89	77
	5	Smokers: 11–39 cigarettes/day	84	86	76	68
	6	Smokers: >40 cigarettes/day	82	77	72	60
Female	1	Nonsmokers, no smoky environment	102	104	108	112
	2	Nonsmokers, smoky environment	98	99	93	85
	3	Smokers not inhaling	97	99	92	85
	4	Smokers: 1–10 cigarettes/day	96	98	89	83
	5	Smokers: 11–39 cigarettes/day	85	85	78	69
	6	Smokers: >40 cigarettes/day	78	80	72	62

*Data from White & Froeb (1980).
†Exposure to a smoky environment or consumption of cigarettes was for more than 20 yr. Group 3 includes pipe, cigar or cigarette smokers who did not inhale. Groups 4, 5 and 6 were all inhaling cigarette smokers.

Newer evidence

Effects on the small airways

In the last 2 years, some new evidence has caused a considerable amount of rethought on the passive-smoking issue. The first such evidence, published in the *New England Journal of Medicine* in March 1980, came from a study by White & Froeb (1980) of the relationship between various pulmonary function indices and passive smoking. A group of 3002 men and women who had been physiologically evaluated during a "physical fitness profile" course, and who were without a history of relevant cardiorespiratory disease, occupational exposure to dust or fumes or severe exposure to pollution at home or at work were divided into six groups according to their exposure to tobacco smoke. No significant difference was found between nonsmokers exposed to a smoky environment for more than 20 years (group 2) and nonsmokers never so exposed (group 1) as regards forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV$_1$); but nonsmokers exposed to passive smoke had statistically significant reductions in forced mid-expiratory flow (FEF 25 to 75%) and in forced end-expiratory flow (FEF 75 to 85%; Table 2).

The most surprising thing about the results of White & Froeb (1980) was that the reductions in FEF seen in group 2 were generally very similar to those seen in group 4, smokers of one to ten cigarettes per day for more than 20 years. Why should a relatively large difference (group 2 *v.* group 1) in airways dysfunction be seen as a result of an apparently relative small difference in exposure to smoke constituents when only a relatively small difference (group 4 *v.* group 2) is seen in response to what was in all probability a much larger difference in exposure?

In view of this implausible result considerable attention had to be given to the details of the study and a number of criticisms were voiced in the *New England Journal of Medicine* (Adlkofer, Scherer & Weimann, 1980; Aviado, 1980; Huber, 1980). One of the oddest things about the study was the procedure by which the sample was selected. It was stated that each candidate was classified into one of the six defined groups. Yet it is clear from Table 2 that anyone who changed smoking habits in the last 20 years does not fit into any group. Furthermore, as the authors define both groups 1 and 2 as living in a house where tobacco smoking was not permitted, what has happened to those nonsmokers, presumably in the great majority, who lived in a house where it was permitted? There are other less important omissions too (inhaling pipe and cigar smokers or cigarette smokers not allowed to smoke at work) and one might even consider it harder to find people who do fit into the groups of White & Froeb (1980) than to find ones who do not. Without an adequate explanation of this anomaly, it is difficult to have much confidence in these findings.

Lung cancer

Whilst the findings of White & Froeb (1980) relate to an index which is contentious and certainly not an accepted reliable indicator of an increased health risk, two more studies published in January 1981, by Hirayama (1981a) and by Trichopoulos, Kalandidi, Sparros & McMahon (1981), caused more attention, as both claimed that nonsmoking wives of smokers had a significantly greater risk of lung cancer than nonsmoking wives of nonsmokers.

Japanese study. Of the two studies, that by Hirayama (1981a), who followed up 91,540 Japanese nonsmoking married women aged 40 years or over in 1965 for 14 years, is the more substantial. He classified women into three groups according to the smoking habits of the husband. The results showed a highly significant trend in the risk of lung cancer with increasing smoking by the husband, with wives of heavy smokers having double the risk of wives of nonsmokers (Table 3). In contrast the wives of smokers had no significant increase in risk for emphysema, asthma, ischaemic heart disease, or cancer of the cervix or stomach.

Following critical comments by Grundmann, Müller & Winter (1981), Kornegay & Kastenbaum (1981), Macdonald (1981), Rutsch (1981) and Sterling (1981), further information on the detail of his study has been given by Hirayama (1981b, 1981c). It is useful to summarize briefly the main points raised and to consider their implications.

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Table 3. *Age-occupation standardized lung cancer risk in Japanese women nonsmokers**

Smoking habit of husband	Sample size	Number of lung cancer deaths	Annual lung cancer mortality rate per 100,000	Standardized lung cancer risk ratio	Significance of trend
Nonsmokers or occasional smokers	21,895	32	8·7	1·00	–
Ex-smokers or smokers of 1–19 cigarettes/day	44,184	86	14·0	1·61	$\chi^2 = 10·88$†
Smokers of ≥ 20 cigarettes/day	25,461	56	18·1	2·08	$P = 0·001$

*Data from Hirayama (1981a).
†One degree of freedom test statistic scoring 0, 1 and 2 for the three smoking categories.

(1) It was suggested that the statistically significant χ^2 value of 10·88 shown in Table 3 might be the result of an arithmetical error as calculations by Mantel (1981), based on the unstandardized data given in the original paper, gave a χ^2 value of only 3·31 which was not significant. In fact the confusion appears to have arisen because Hirayama (1981a) had standardized for age and occupation but had not stated this clearly. This was important as the husbands who smoked were younger than those who did not. In a subsequent letter Hirayama (1981c) presented data by age and occupation which allowed one to calculate a χ^2 value of 8·70 which, while not the same as that originally quoted, was similar and significant. Surprisingly, in the same letter, Hirayama (1981c) quoted a much higher χ^2 value of 36·81 for a similar comparison (difference between nonsmoking women whose husbands have never smoked and those whose husbands have ever smoked) but this was based on a statistical error (Lee, 1981). Despite this error, it seems probable that the association found really was a significant one, though of course a significant association need not imply a significant causal effect of passive smoke exposure.

(2) For a reason that was not apparent, Hirayama (1981a) standardized for age of the husband and not for the age of the wife. However it seems unlikely this would have materially affected the findings, as, if it did cause bias, it would be expected to affect all the causes of death and not just lung cancer.

(3) Smoking habits were determined only at the beginning of the period and may have changed. Again, however, it seems unlikely that enough of these women would have taken up smoking to cause marked bias.

(4) The great majority of the lung cancers seen, 17 out of 23 in a sample, were adenocarcinomas, a type of lung cancer generally believed to be much more weakly related to smoking than squamous cell carcinoma.

(5) Evidence of trends in lung cancer rates in Japan suggest that there may be some other important cause of lung cancer which was not studied. Between 1947 and 1978, female lung cancer rates rose nine-fold and yet Hirayama's (1981a) own results show only a four-fold risk in active cigarette smokers compared with non-passively exposed nonsmokers—and relatively few women in Japan (about 15%) smoke anyway.

(6) The index of "passive" exposure used is not likely to be very accurate. Not only does the husband smoke a varying proportion of his cigarettes at home, but the wife will also be exposed to other sources of exposure besides the husband. In principle, though, this is likely to underestimate rather than overestimate any relative risk associated with passive smoking.

(7) What is most surprising, however, is the sheer magnitude of the association. The two-fold increased risk in wives of heavier smokers is similar, in Hirayama's (1981a) study, to that of women actively smoking about five cigarettes a day, whilst it was stated that the heavy smokers smoked on average only 8·4 cigarettes a day at home and these presumably not all in the direct presence of the wife. If this is so, the study seems to be suggesting that one actively smoked cigarette is not so very different from one passively smoked one, which seems completely inconsistent with the dosimetry, especially when one realises that an active smoker probably has greater passive smoke exposure than a passively exposed nonsmoker.

Greek study. In contrast to the Japanese study, the small Greek case-control study of Trichopoulos *et al.* (1981) is relatively lightweight, being based on only 40 lung cancer cases seen in nonsmoking women. However, their results (Table 4), though having quite wide confidence limits, agree well with those of Hirayama (1981a). Taking into account a number of possible confounding factors (age, duration of marriage, occupation, schooling, residence) did not affect the general picture.

Although the trend is statistically significant, the limitations pointed out by the authors—the small number of cases, 35% of which were not cytologically confirmed, and the cases and controls being taken from different hospitals—would have meant that no great weight would have been attached to the results had they not come out at the same time as, and being supported by, those of Hirayama (1981a). It is interesting, in comparison with the Japanese study, that Trichopoulos *et al.* (1981) specifically excluded adenocarcinomas from their cases, since it was presumably implicitly assumed that this type of lung cancer was not smoking-associated.

American study. Even taken together, the Japanese and Greek studies are by no means totally convincing. Doubts as to whether such a large effect on lung cancer incidence could possibly be due to such an apparently small dose of tobacco smoke have very recently been supported by Garfinkel (1981) based on

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Table 4. *Smoking habits of husbands of Greek nonsmoking women with lung cancer and of nonsmoking control women**

Smoking habit of husband		Lung cancer cases	Controls	Relative risk	Significance of trend
Nonsmokers		11	71	1·0	
Ex-smokers		6	22	1·8	
Smokers (cigarettes/day):	1–10	2	9	2·4	$\chi^2 = 6{\cdot}45$
	11–20	13	32		
	21–30	4	6	3·4	$P < 0{\cdot}02$
	>30	4	9		
	Total	40	149		

*Data from Trichopoulous, Kalandidi, Sparros & MacMahon (1981).

results from the American Cancer Society's million person prospective study and the US Veterans Study. Two analyses were carried out. The first, similar to that used in the Japanese and Greek studies, showed no significant relationship between lung cancer risk and the smoking habit of the husband (Table 5). Indeed, after matching for age, occupation, education, race, urban/rural residence and absence of serious disease at the start of the study, nonsmoking women married to smokers of 20 or more cigarettes a day had an estimated risk of lung cancer virtually identical to that of non-smoking women married to nonsmokers.

The second analysis found no evidence of any trend in lung cancer rates in nonsmokers over the period of either study. As death rates of smokers had increased substantially over the period, presumably mainly because of the duration of smoking effect (older smokers at the end of the period would on average have smoked for longer than similar aged smokers at the beginning of the period), one might have expected a similar rise to be seen in non-smokers, had passive smoking been a material cause of lung cancer risk in non-smokers.

Although one might argue that passive-smoking effects would be more difficult to pick up in the USA where women spend more time out of the home and marry more often [Garfinkel (1981) had no data on smoking habits of ex-husbands] than is the case in Greece or Japan, it is clear that the Garfinkel (1981) study has underlined the view that further studies are needed to explore the relationship between passive smoking and lung cancer.

Both Garfinkel (1981), and also Hammond & Selikoff (1981) in a paper reviewing findings from the Japanese and Greek studies, pointed out that it is extremely difficult to reconcile findings indicating a higher risk of lung cancer in passive smoking with results from the study by Auerbach, Garfinkel & Hammond (1979) of histological changes in bronchial epithelium taken from autopsy material. Lesions frequently seen in cigarette smokers (such as atypical nuclei and lesions similar to carcinoma *in situ*) have very rarely been found in people who have never smoked. This finding, and also the reported small doses of smoke received by nonsmokers, both suggest that passive smoking cannot play more than a very small role in the development of lung cancer, a view also reached by Lehnert (1981) who considered evidence from the USA and Japanese studies in detail. If passive smoking is not causally implicated it is of fundamental importance to try to identify the confounding or biassing factors that resulted in the higher risk of lung cancer seen in wives of smokers in the Japanese and Greek studies, but not in the American study.

Conclusion

While more research is certainly needed, there seems at present to be no convincing evidence that passive smoking results in any material risk of serious disease for the healthy nonsmoker.

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Table 5. *Lung cancer deaths amongst nonsmoking women in the USA**

Smoking habit of husband	Number of lung cancer deaths	Age standardized analysis mortality ratio	Matched group analysis mortality ratio
Nonsmoker	65	1·00	1·00
Smoker: <20 cigarettes/day	39	1·27	1·37
Smoker: ≥20 cigarettes/day	49	1·10	1·04

*Data from Garfinkel (1981).

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AGE AS A MODIFYING FACTOR IN THE ASSOCIATION BETWEEN LUNG CANCER IN NON-SMOKING WOMEN AND THEIR HUSBANDS SMOKING STATUS

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ABSTRACT:

A previous analysis (1) of (2) is reviewed and extended. Age is shown to be an important modifying factor in the association between lung cancer in nonsmoking women and their husbands' smoking status. Heterogeneity of the cell specific risk ratios is demonstrated using the Mantel-Haenszel extended test for trend, when the data are stratified by the wife's age. The lack of fit of the multiplicative model contra-indicates the use of a Mantel-Haenszel summary statistic. It is likely that age at entry is confounded with calendar period increases in lung cancer mortality in nonsmoking women.

INTRODUCTION

Hirayama reports (2) on a longitudinal record linkage study of married women who, in 1965, were reported to be nonsmokers. Deaths in the period 1966 to 1981 were linked to a questionnaire given in 1965. In this manner, the cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife to produce the results reported (2). His paper presents the mortality experience of nonsmoking wives by selected causes of death cross-classified by husband's smoking status, husband's drinking status, husband's occupation, green and yellow vegetables daily and husband's age. Here, we restrict our attention to Tables 1 & 2 of (2) in order to focus on the effect of standardizing by husband's age rather than by the wife's age when studying the association between these women's lung cancer deaths and their husbands' smoking status.

An earlier paper (1), based on a standard Poisson regression and using the conventional 5% level of significance, indicates, on the basis of these published tables, that

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- husband's smoking is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline statistical significance and dependent on the presence or absence of other factors in the model and the classification of the husband's smoking at entry.

- that husband's drinking habit shows no significant association with his wife's lung cancer mortality.

- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality.

In contrast, it is concluded in (2) that there is 'a significantly increased risk of' lung cancer mortality 'in relation to the extent of the husband's smoking... The association was significant when observed by age of husbands .. and also by age of wives.'

Tables 1 and 2 of (2) give different tabulations of the 16 years lung cancer mortality in these nonsmoking wives. Table 1 gives the lung cancer death rates by five levels of husband's smoking at entry (Non, Ex, 1-14/d, 15-19/d, 20+/d). Table 2 collapses this to Non, Ex. or 1-19/day, 20+/day, here called Non, Light and Heavy ETS exposure. Table 1 further stratifies the wives' lung cancer death rates by the husband's age at entry whereas Table 2 stratifies by the wife's age at entry. (Since it is the usual practice to adjust for the subject's age rather than her husband's, it is remarkable that this is the only occasion in which Dr Hirayama has adjusted wife's mortality by her own age rather than that of her husband's).

Exhibit 1 summarizes a 'power' model analysis of Tables 1 and 2. The power transform finds the best model within a family of loglinear models which include the multiplicative and additive models. Exhibit 1 shows the residual deviance after fitting the factors for age and ETS exposure to Tables 1 and 2 of (2). Table 1 shows little discrimination among models, all giving good fits. Table 2, in contrast, shows that the additive model fits better than the multiplicative model. Indeed, the best fitting power model has a power of $\rho = 1.14$ which is *beyond* the additive for which $\rho = 1.0$. (The multiplicative model in turn corresponds to a $\rho = 0$). However, all models of Table 1 are better fitting than the best fitting model for Table 2, suggesting that further stratification in five year groups may be necessary to adjust for age or that other covariates may be important.

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Exhibit 1

Deviances (df) for additive, multiplicative and best fitting power models

	MODEL		
TABLE	ADDITIVE	POWER	MULTIPLICATIVE
Table 1	3.79 (12)	2.76 (12)	3.24 (12)
Table 2	7.91 (6)	7.85 (6)	10.72 (6)

Model is 1+ Husband's Age(4)+ ETS(5) for Table 1

.... 1+ Wife's Age(4)+ ETS(3) for Table 2

Outcome analyzed is cumulative Lung Cancer Death Rate (1966-1981)

The additive model provided a superior fit when wife's age is used to stratify as in Table 2. This means that risk ratios for ETS exposure change with age at entry. The additive model assumes that a constant excess risk is added to the age dependent death rate from lung cancer. Thus, the substitution of husband's age for wife's age changes the underlying model from the multiplicative to the additive and the appropriate summary statistic from a risk ratio to an excess risk.

The analysis given by (1) of (2) was that recommended by Breslow & Day (3) for cohort studies. Dr Hirayama, however, presents his results in terms of the older and more limited Mantel-Haenszel statistics. Here, we follow (2) in presenting a 'classical' analysis of his results in order to show what Dr Hirayama *might* have reported with the techniques available to him at that time, if the data had been stratified by the subject's age at entry rather than by spousal age.

RESULTS

Hirayama's analysis treats Table 2 as a 2x4x3 contingency table where wives are classified as either having died from lung cancer or not, and are

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then further tabulated in 4 ten year age groups by wife's age in 1965 and by 3 levels of husband's cigarette smoking (as reported in 1965).

He analyzes Table 2 by comparing the base line exposure in each age group, Non with Light and Non with Heavy ETS exposures. In other words, Hirayama treats Table 2 as though it were two 2x2x4 tables.

He then presents point estimates of the summary risk ratio for Table 2, and tests for the significance of the weighted risk ratio but omits tests for the homogeneity of the age-specific risk ratios which form his Mantel-Haenszel estimate. (A significant test of homogeneity indicates that the use of the weighted estimate is contra-indicated in that the age-specific risk ratios differ significantly).

Here, we collapse the five ETS levels in Table 1 to Non, Light and Heavy in order to have a similar configuration to Table 2. Now the only difference between (collapsed) Table 1 and Table 2 is the use of husband's age in Table 1 and the the use of wife's age in Table 2.

Exhibit 2

Table 1 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
	40–49	1.55	2.32	1.87
HUSBAND'S	50–59	1.54	1.90	1.68
AGE AT	60–69	1.53	1.96	1.64
ENTRY	70–79	0.71	0.67	0.70
χ^2_{trend}	df=1	0.34	5.6	0.71
$\chi^2_{common\ \psi}$	df=3	1.39	1.13	2.03
$\chi^2_{\psi_{MH}=1}$	df=1	3.16	8.53	5.70
ψ_{MH}		1.43	1.90	1.57

Using the classical Mantel-Haenszel methodology for stratified data, the results of the power modelling on Table 1 were confirmed. Thus, see Exhibit 2, stratification by husband's age and the three levels of ETS exposure (Non, Ex. or 1-19/day , 20+/day, called Non, Light and Heavy here, yielded risk ratios that were reasonably constant across age strata. Testing the

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homogeneity of the age-specific risk ratios across the four age strata yielded a homogeneity chi-square on 3 degrees of freedom (χ^2_3) that is not significant at either level of the ETS exposure or at both levels combined (Non vs Exposed).

The test of homogeneity in common use is not powerful (4), especially when applied in this manner to cohort data. A more complete treatment of the test for heterogeneity, as applied to cohort studies, is given in (3). Note, however, that we restrict ourselves to the case-control version of the Mantel-Haenszel approach in order to mirror Dr Hirayama's form of analysis.

A test for trend in the risk ratio over age, based on 1 degree of freedom, is provided here for comparability with the analysis which follows. Exhibit 2 shows that the trend test is not significant, with the possible exception of Non vs Heavy (but the value 5.6 is unstable and may be discounted).

Exhibit 3

Table 2 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
	40–49	2.38	3.30	2.76
WIFE'S	50–59	1.60	1.92	1.72
AGE AT	60–69	1.15	1.02	1.12
ENTRY	70–79	0.09	0.48	0.19
χ^2_{trend}	df=1	4.34	5.48	7.64
$\chi^2_{common\ \psi}$	df=3	11.94	5.41	11.24
$\chi^2_{\psi_{MH}=1}$	df=1	2.28	5.15	3.88
ψ_{MH}		1.36	1.66	1.45

In contrast to the above analysis, a strong statistical interaction between age and ETS exposure (Exhibit 3) is evident when the data are stratified by wife's age. The chi square test for homogeneity is statistically significant ($P < .05$) when comparing Non to Exposed across age, as is the comparison between Non and Light ($P < .01$). The comparison between Non and Heavy ETS exposure (20+/day) is not statistically significant. The Mantel-Haenszel extension test to evaluate trends across *age* for each level of the

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husband's smoking status is statistically significant ($P < .05$) at all exposure levels. This indicates a true decrease in the risk ratios with increasing wife's age. Indeed, the statistical significance or P value of the trend over wife's age is of the same order as the trend for a " dose response" relationship between the lung cancer death rate and the husband's smoking status.

These results compare favorably with the results from the more general power analysis. This underscores the need, when doing the classical Mantel-Haenszel analysis, to *first* test the assumption of a common risk ratio before proceeding to use the Mantel-Haenszel summary estimate. If the assumption of a common risk ratio is untenable, it is wrong to proceed to calculate and test the significance of a global estimate. "In this situation, it is more important to try to understand and describe the sources of variation in the relative risk than simply to provide a summary measure" (4, p.138).

Our conclusion, presented at Tokyo, was that the multiplicative model which is implicit in the use of the risk ratio is contra-indicated. The relationship between ETS exposure and lung cancer mortality was demonstrated in these data as best described by the additive model. This leads to 'excess risk' as the appropriate summary statistic.

The lack of fit of the multiplicative model may be seen directly from an examination of the risk ratios by age group. Under the multiplicative model, the risk ratio is assumed to be constant over age, apart from random sampling error. Exhibit 3 shows that the risk ratio falls dramatically with age for Non vs Light, Non vs Heavy and Non vs Exposed. It is unexpected to find such a radical shift in the underlying model, given the stated equivalence in the age structures of husband and wife.

DISCUSSION

The Mantel-Haenszel analysis used in (2) implicitly assumes a multiplicative model. This, in turn, is based on the assumption that the risk ratio for ETS exposure and lung cancer mortality in nonsmoking wives is relatively constant over a 40 year age range in the cohort and over the 16 years of follow-up. This assumption could have been tested in (2) on Table 2 with the techniques available at that time. Here, in our analyses, both the Mantel-Haenszel tests for trend and the commonly used test of homogeneity over strata (4), show a clear indication that the multiplicative model does not hold when the wife's age is used to stratify her cumulative lung cancer mortality covering 16 years.

Age at entry effects encompass both chronological age and cohort differences. In the light of the current finding that the risk ratio falls with age at entry, it is also likely that risk ratios would be found to fall with calendar time.

If tests for a common risk ratio by wife's age at entry had not been statistically significant, then Dr Hirayama's substitution of husband's age for wife's age would have had few implications. But since this switch has been shown to change the underlying statistical model and summary statistic, it is clear that husband's age cannot be use as a proxy for wife's age. There is indeed no good reason to do so as wife's age was recorded along with husband's age at entry to the study in 1965. Since Table 2 is the only occasion on which the wife's age is given, we cannot investigate possible interactions of wife's age with other covariates used by Dr Hirayama in this study. Other causes of death in women are also stratified by husband's age. Thus, we are unable to verify whether the current anomaly exists for other causes of death. It is therefore unknown whether husband's age is a satisfactory surrogate for wife's age in any of those papers by Hirayama which deal with female mortality.

Lung cancer mortality in these nonsmoking wives has been shown to be low compared with the Japanese population (1). This may be true of all female mortality results from this study.

It has been pointed out (1) that stratification by age into 4 ten year age groups may result in substantial residual confounding. Whether stratification was based on husband's or wife's age is irrelevant, since, when "the stratification is too coarse, ... some confounding may remain" (4, p.99). How much of the interaction identified in Exhibit 3 using wife's age might be attributable to an inadequate control of age is unknown. Further, as a consequence of the poor fit of the multiplicative model in that analysis, age and calendar time interaction cannot be ruled out as contributing to a potentially spurious association between lung cancer mortality and ETS. We affirm Breslow & Day's suggestion (3) that five year age groups be used and, that "for a long study, it is appropriate to partition the time axis into several intervals" (4, p.201). A true cohort study would report the duration of ETS as well as the (presumed) daily exposure and would use each subject's person-years of follow-up as the denominator in rate calculations and risk analysis. From Dr Hirayama's written descriptions of his study, such information is in his files or is available by linking a couple's initial questionnaire and death certificates.

SUMMARY & CONCLUSIONS

With the exception of Table 2 of (2), husband's age has been used to adjust for wife's mortality in a large and often quoted record linkage study in Japan 1966-1981. Our analysis shows that husband's age is *not* a surrogate for wife's age, in spite of its common use as such by Dr Hirayama. Since age at entry is confounded with cohort effects, it is also likely further that interactions occur between age and calendar period and between age and other covariates not represented in the model.

As a consequence of this finding, our conclusion is that the results of Hirayama's large study on ETS and lung cancer should *not* be pooled with other ETS/lung cancer studies to form a global estimate of relative risk. The relevance of this Japanese study's findings to public policy is questioned in the absence of more detailed information on exposure and follow-up, and more extensive analysis of the data at the level of the individual subject.

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Present and future of indoor air quality.
C.J. Bieva, Y. Courtois, M. Govaerts, editors.

AN EXAMPLE OF EXTRA-POISSON VARIATION SUGGESTING AN UNDER-SPECIFIED MODEL.

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INTRODUCTION

There is now an extensive literature on environmental tobacco smoke (ETS). Several meta-analyses of this literature have combined risk estimates for lung cancer from different studies weighted by the quality and size of the study. Thus, in their meta-analysis, Letzel et al. (1988) give various scenarios which use different figures from Hirayama's study, depending on whether the husband's or wife's age was used to adjust the wife's cumulative mortality. Since Hirayama's study constitutes about 20% of all lung cancer deaths in the ETS literature, it is important to use the correct relative risk from Hirayama in constructing global estimates. Here, it is shown that a proper analysis of Hirayama's study leads to a non-significant association between ETS and the risk of death from lung cancer in non-smoking wives.

Hirayama (1981) reports an age standardised risk ratio of 1.90 for lung cancer among non-smoking women married to heavy smokers and finds a highly significant trend ($P < 0.001$) between the amount smoked by husbands and the lung cancer mortality of their non-smoking wives. He also interprets this association as arising from a causal relationship between husband's smoking and wife's lung cancer:

> These results indicate the possible importance of passive or indirect smoking as one of the causal factors of lung cancer.
> (Hirayama, 1981)

THE STUDY

Dr. Hirayama's study links deaths from all causes occurring in the period 1966 -1981 to a questionnaire given in late 1965 to approximately 250.000 Japanese adults. Almost all those over age 40 in 29 Health Center Districts in 6 Japanese prefectures who were 'generally healthy' (Hirayama, 1978) were interviewed. At that time, each respondent was asked for his or her current smoking status. Although not originally designed as a study of the association between passive smoking and health, Dr. Hirayama subsequently linked the mortality of wives who were classified as non-smokers with their husband's smoking status and, if he was a smoker, with the amount smoked.

Hirayama's smoking classification is based on only one question at the time of the survey as to whether the respondent smoked, and, if so, smoked daily. The respondent was also asked whether he/she smoked occasionally, was an exsmoker, a non-smoker or an 'obscure' smoker. The age at which smoking started was recorded where appropriate. Husband's smoking status in 1965 was treated as an index of wife's ETS exposure. No direct measure of ETS exposure was made. In the following, ETS refers to this surrogate for passive smoking, i.e. the self-reported classification of a husband's smoking in 1965 when his wife was reported to be a

non-smoker. In Hirayama's 1981 paper there was some ambiguity as to how he had treated the data. The estimates made by Hirayama of the association of ETS and lung cancer lead him to conclude:

> The relation between the husband's smoking and the wife's risk of developing lung cancer showed a similar pattern when analysed by age and occupation of the husband. (Hirayama 1981)

In response to his 1981 paper, a number of methodological questions were raised. In particular, Hirayama's use of the husband's age to adjust the wife's mortality was questioned.

> It is also not clear ... whether you standardised on the age of the wives themselves. Such calculations ... would certainly make the analysis more conclusive. (Harris & Du Mouchel. 1981)

Some years later, Hirayama responded to this criticism by analysing the wife's lung cancer mortality adjusted by the wife's age. In Hirayama (1984) the relative risk of 1.9, reported earlier, for non-smoking wives married to 'heavy' cigarette smokers drops to 1.7 when adjusted by wife's age. He concludes:

> There was a statistically significant increased risk [of lung cancer among non-smoking wives] in relation to the extent of the husband's smoking ... the association was significant when observed by age of husbands (table 1) and also by age of wives (table 2). (Hirayama, 1984 p.179)

THE DATA

Hirayama (1984) gives the lung cancer death rates in the period 1966-1981 for 91.540 self-reported non-smoking wives cross-classified by husband's smoking and by husband's age (Table 1) or wife's age (Table 2). In both tables, age is given in four 10 year age groups. Table 1 gives husband's smoking classified into 5 levels by the amount smoked daily.

TABLE 1

LUNG CANCER DEATH RATES per 1000 (1966-1981)
from Hirayama (1984)

		HUSBAND'S SMOKING				
		Non	Ex	1 – 14/d	15 – 19/d	20 + /d
	40–49	0.6	0.8	0.9	1.2	1.5
HUSBAND'S	50–59	1.3	1.6	2.1	2.0	2.4
AGE	60–69	2.5	4.1	3.9	3.6	4.9
	70–79	6.6	5.7	3.3	9.5	4.4

In order to make direct comparisons between the effect of adjusting by husband's or wife's age, Table 1 is collapsed to Table 1A. using the same grouping for husband's smoking as in Table 2, here called Non, Light and Heavy.

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TABLE 1A

LUNG CANCER DEATH RATES per 1000 (1966-1981) AND SAMPLE SIZE n (000) adapted from Hirayama (1984) Table 1

Husband's Age	Husband's smoking: Non Rate	n	Light Rate	n	Heavy Rate	n
40-49	0.6	6.2	1.0	15.0	1.5	10.8
50-59	1.3	7.8	2.0	15.6	2.4	9.8
60-69	2.5	7.1	3.9	12.4	4.9	4.7
70-79	6.6	0.8	4.7	1.1	4.4	0.2

TABLE 2

LUNG CANCER DEATH RATES per 1000 (1966-1981) AND SAMPLE SIZE n (000) from Hirayama (1984)

Wife's Age	Husband's smoking: Non Rate	n	Light Rate	n	Heavy Rate	n
40-49	0.5	7.9	1.2	17.5	1.7	12.6
50-59	1.8	7.6	2.9	15.6	3.5	8.8
60-69	2.6	6.2	3.0	10.4	2.6	3.8
70-79	17.4	0.2	1.5	0.7	8.4	0.2

Note that, in this paper, Table 1A and Table 2 of Hirayama (1984) are both 4 by 3 contingency tables, based on the mortality experience of the same 91,540 women.

MODELLING

The analysis of Table 1A and 2 is usually done using a fixed effects loglinear or logistic model (Breslow & Day 1986). These in turn are viewed as particular examples of a generalized linear model which may be misspecified in three ways

- the linear predictor may be incomplete or incorrect and or
- the wrong link may be used and/or
- the wrong error structure may be assumed.

In epidemiological investigations, the linear predictor is often incomplete in that important covariates are omitted or measured from the wrong origin or in the wrong scale. Such is likely to be the case here in that no allowance is made for diet, for cohort or period effects or for the duration and amount of ETS exposure, either before or after 1965.

As its name implies the loglinear model uses a linear predictor to fit the logarithm of the cumulative mortality rates. Here it is shown that a model allowing for extra-Poisson variation is necessary and that this model leads to a non-significant effect for ETS in Table 2.

The usual regression model relating interval or measurable quantities such as height and weight, assumes a normal distribution of errors about the regression line. By contrast, the loglinear model assumes a Poisson distribution of errors between the observed and fitted

log(rates). The Poisson distribution, in turn, implies that the mean of the distribution equals the variance or dispersion of the distribution. In other words, the usual model for mortality rates estimates only the mean. Recently, this assumption has been called into question.

> Techniques like regression analysis ... have traditionally focussed attention on modelling and analysis of means or location parameters. Scale parameters have been regarded as nuisance parameters; interest in them has been largely limited to testing the equality of variances so that techniques that assume variance homogeneity can be applied. Recently, however, there has been more interest among statisticians in the structural modelling of variances and in the estimation of dispersion effects. (Anon., the American Statistical Association. 1986)

In the same year in which Hirayama published his only tabulation in which wife's age is used (Table 2 of Hirayama, 1984), Breslow (1984) published a method by which an extra term σ^2 could be added to the loglinear model to allow for excess variation beyond that assumed by a fixed effects model. The model for extra-Poisson variation is shown below to be an extension of the loglinear model.

If d_i deaths are observed among n_i wives, such that $E(d_i) = n_i\lambda_i$ for different subgroups i, then the loglinear model assumes that d_i follows a Poisson distribution with mean $n_i\lambda_i$, where d_i is related to a linear predictor via a logarithmic link or transformation

$E\, ln(d_i/n_i) = x_i\beta$.

In contrast, the extra-Poisson variation model assumes that

$E(d_i) = \mu_i \approx exp\, ln(n_i) - x_i\beta$

where β is a column vector of unknown regression parameters and where

$var(d_i) \approx \mu_i - \sigma^2\mu_i^2$.

The extra-Poisson variance, σ^2, is determined by an iterative re-weighting technique (Breslow 1984). Note that if there is no over-dispersion, σ^2 is estimated as zero.

RESULTS

The usual loglinear model fits Table 1A better than Table 2. Conventionally, a good fit is one for which the residual deviance is less than the degrees of freedom remaining after fitting the linear predictor. The residual deviance after fitting the same linear predictor, age plus husband's smoking level, is 2.0 in Table 1A and 10.7 in Table 2. Since Table 1A has been configured to have the same dimensions as Table 2, both of these deviances may be evaluated against 6, the number of degrees of freedom which remain after fitting age and husband's smoking. In summary then, the deviance for Table 1A is 2.0 with 6 d.f. as compared with a deviance of 10.7 with 6 d.f. for Table 2.

This is paradoxical. Why should the use of the wife's age give a worse fit than the husband's age when modelling the wife's lung cancer mortality? Since this is contrary to our expectation, it suggests that the model is incorrect in one or more of the three categories listed above: incorrect linear predictor, link or error structure.

To allow for the possibility of over-dispersion, Table 1A and Table 2 have been analyzed using the extra-Poisson loglinear model. σ^2 is estimated as zero in Table 1A and as 0.23 in Table 2. An approximate test for the significance of this estimated over-dispersion is to compare the square root of the reduction in deviance after fitting σ^2 with a one-sided Normal distribution. Such a test has an associated probability of 0.015. There is thus some support for the use of this model (and its conclusions) in preference to the fixed effects model. Moreover,

It is not necessary that σ be significant in order to stay in the model. Often the data are suggestive a priori of excess variation and a prudent analysis will account for it even if not significant. (Mauritsen, 1988)

TABLE 3

EFFECT OF MODEL CHOICE ON P VALUES FOR ETS AS A FACTOR OR A TREND

MODEL		LOGLINEAR	EXTRA-POISSON
TABLE 1A	FACTOR	.01	.01
	TREND	.003	.003
TABLE 2	FACTOR	.05	.63
	TREND	.02	.37

Table 3 shows that this change of model has no effect in Table 1 in which husband's age is used. ETS is statistically significant, both as a factor ($P = 0.01$) and as a trend ($P = .003$) in Table 1A. Nevertheless, the change of model has a marked effect in Table 2 in which the wife's age is used. The ETS factor in Table 2 which is barely significant ($P = 0.05$) under the loglinear model is clearly not significant under the extra-Poisson model ($P = 0.63$). It is inappropriate to test for a trend before the factor has been shown to be significant, in the absence of a prior hypothesis for trend. However, here, following Dr. Hirayama, the trend of the relative risk against the level of ETS is tested. The ETS trend of log (relative risks) with husband's smoking (non, light and heavy) which was just significant ($P = 0.02$) is now, under the model for extra-Poisson variation, not a significant trend ($P = 0.37$).

TABLE 4

EFFECT OF MODEL CHOICE ON 95% CONFIDENCE LEVELS FOR ETS RELATIVE RISKS

MODEL		LOGLINEAR	EXTRA-POISSON
TABLE 1A	LIGHT	0.96-2.08	0.98-2.08
	HEAVY	1.24-2.81	1.24-2.81
TABLE 2	LIGHT	0.92-1.97	0.49-2.51
	HEAVY	1.10-2.48	0.64-3.41

An alternative way of showing the effect of making the model more general is to display the 95% confidence limits for specific levels of ETS exposure. As is seen in Table 4, the model choice has no effect on 95% confidence limits in Table 1A, being 0.98 – 2.08 for the Light vs Non relative risk and 1.24 – 2.81 for the Heavy vs Non relative risk. The choice of model however does affect the 95% confidence limits in Table 2. Here, the Light vs Non relative risk changes from 0.92 – 1.97 to 0.49 – 2.51, neither of which are statistically significant, since both contain the non-effect level of 1.0. The Heavy vs Non relative risk in Table 2 changes from 1.10 – 2.48 to 0.64 – 3.41, so that the interpretation of this association also changes from statistically significant to nonsignificant. Thus, even when the husband reports smoking 20– cigarettes daily, the non-smoking wife shows no significantly increased risk from passive smoking.

TABLE 5

EFFECT OF MODEL CHOICE ON 95% CONFIDENCE LIMITS FOR ESTIMATES OF ETS TRENDS

MODEL		LOGLINEAR	EXTRA-POISSON
TABLE 1A	TREND	1.11-1.66	1.11-1.66
TABLE 2	TREND	1.05-1.56	0.80-1.87

As shown in Table 5, the 95% confidence limits are consistent with the P values for trend given above. No change is observed in the 95% confidence limits, 1.11 – 1.66, for the trend relative risk in Table 1A. The previously significant trend in Table 2, with 95% confidence limits of 1.05 – 1.56, becomes non-significant with limits of 0.80 – 1.87.

DISCUSSION

Hirayama's analysis assumes that the risk of a lung cancer death is constant within each of the twelve age/exposure sub-groups of Table 2 over the period 1966-1981 and yet:

> Environmental variables are ... difficult to quantify since individual histories vary widely with respect to the onset, duration and intensity of exposure and whether it was continuous or intermittent. (Breslow & Day 1980)

Unfortunately, the danger of using a fixed effects model when unwarranted is that the error term is underestimated:

> Tests of significance and confidence intervals that fail to account for the lack of fit of a given model may be seriously misleading. (Breslow 1987)

Such is the case here. Dr. Hirayama's use of a fixed effects model which gives a poor fit has resulted in his reporting a spuriously significant result. Fitting a more general model confirms that extra-Poisson variation is present in Table 2 (where the wife's age is used) though not in Table 1A (where the husband's age is used instead).

The finding of excess dispersion in this longitudinal record linkage study is likely to be due to the omission of period and cohort effects from the model. Osmond & Gardner (1989) have shown that

> When the assumptions [in the model] are inappropriate, as is usually the case, misleading results will occur.

The period 1966-1981 saw an increasing use of cigarettes in Japan (Kristen 1986) and an increasing mortality from lung cancer in women so that it is unlikely that the association between ETS and lung cancer remained constant over this 16 year period, as is assumed in Hirayama's analysis.

The non-independence of observations within subgroups effectively reduces the sample size, increases the variance and widens the 95% confidence limits for the relative risk of ETS. This is illustrated by the fit of a model allowing extra-Poisson variation, since now the 95% confidence limits include 1.0. In other words, with this model, ETS is no longer significantly associated with lung cancer mortality in non-smoking wives.

No change is observed, however, after fitting the more general model to Table 1A. ETS is still significantly associated with female lung cancer mortality. This is interpreted as being due to the substitution of husband's age for wife's age. Thus, while the linear predictor used in Table 2 (Wife's Age – Husband's Smoking) demonstrates the absence of period and cohort terms through the need to estimate an extra-Poisson variance component. the linear predictor used in Table 1A (Husband's Age – Husband's Smoking) does not. Rather a model which uses Husband's Age is seen as mimicking a model which includes
(Wife's Age + Husband's Smoking + Wife's Cohort + Period Effects).

Recent research supports this interpretation. Logue & Wing (1986) show that record linkage studies which use rates cumulated over 20 years can produce just the effect reported here, an age/exposure interaction. Under these circumstances. the significance of ETS in Table 1A should *not* be interpreted as indicating a causal relationship but simply that the husband's age. together with husband's smoking status, are proxies for other important but unnamed determinants of an observational study over time.

SUMMARY and CONCLUSIONS

If the wife's mortality from lung cancer is adjusted by the husband's age, the loglinear model gives a good fit and husband's smoking has a significant association with lung cancer mortality in non-smoking wives. It is, however, better to adjust by a person's own age. A consequence of using the wife's age to adjust the wife's mortality from lung cancer is that a loglinear model with extra-Poisson variation is required. With this model, the risk factor. 'husband's smoking', is not statistically significant. indicating no increased risk of lung cancer mortality in non-smoking wives of smoking husbands.

Because of this finding. it is important to use the correct analysis of Hirayama's study in future meta-analyses of published ETS studies in order to get a global estimate of the association of spousal smoking with lung cancer death rates in non-smokers. Such an analysis should incorporate the wife's age when the wife's lung cancer mortality is analyzed.

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Model Specification Effects in ETS/Nutrition Research

S. J. Kilpatrick

Summary

In Hirayama's study the average annual death rate for wives aged 60–69 from lung cancer is 18 per 100,000 as compared with 39 for all Japanese women (Exhibit 9). Also, wives aged 50–59 have the same lung cancer death rate as wives aged 60–69 (i.e., no age trend). These results may arise from the 23% of the cohort which is missing.

These anomalies are obscured in Hirayama (1984) by the use, in all but one table (Table 2), of husband's age rather than the wife's age.

Using wife's age to analyze wife's mortality leads to an additive model for lung cancer. The use of the relative risk is thus contra-indicated.

The weak association of husband's smoking status with wife's lung cancer mortality is probably a consequence of incomplete age adjustment when coarse age groups of 10 years are used over a 16-year period. Suggestions are made for further analyses using ungrouped information.

The effect of daily intake of green and yellow vegetables on lung cancer is also reanalyzed. A standard analysis of these data leads to different results than those given by Hirayama (1984).

Public examination of these data is called for to yield independent answers to the questions raised here.

Introduction

Hirayama (1984) reports on a longitudinal record linkage study of married women who, in 1965, were reported to be non-smokers. Interviews using form 1 (see Exhibit 1) were carried out October through December 1965 of persons 40 years and above in 49 districts in 29 health center districts in Japan. In 1971, a 3% sample of those subjects were re-interviewed (Hirayama 1982) using form 2 (Exhibit 2). Form 2 is form 1 with additional questions on current health status and illnesses in the past five years. A second follow up was apparently done between 1971 and 1983 since Hirayama (1984) refers to a recent study of 410 males and 158 females in Aichi province. Apart from these, no monitoring of the population was carried out apart from linking deaths in the period 1966 to 1981 to the original questionnaire (Exhibit 1).

The cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife. In the sequel it is important to note that date of birth, age of first marriage, age started smoking and date of death are recorded. Linkage of a married couple's original responses to the wife's death certificate can therefore yield the woman's precise age at entry. Likewise, for a non-smoking wife, the

H. Kasuga (Ed.) Indoor Air Quality

Exhibit 1

Form 1 Initial survey

Health Questionnaire Name of Prefecture Health Center

District code		Household code	Individual code
Name	M F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed	
Address			
Place of birth	Prefecture	City	Occupation (in detail)
For women	Number of children	Length of breast feeding after last delivery month(s)	Age at first marriage

Anamnesis

Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2 Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kizami (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2. Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure

age at which the husband started smoking and the date of the marriage can yield the duration of exposure to husband's cigarette smoke at the first interview.

The data from this study as presented by Hirayama (1984) has been summarized in 10 tables for non-smoking wives. Exhibit 3 lists these tables and shows by table number the cause of death and the factors by which the cause of specific death rates are classified. The levels of a given factor are given in parentheses. Note that Table 5 is a collapsed form of Table 6 or of Table 10 and Table 7(1) of Table 7(2). Note that Table 9 is Table 8 omitting non-smoking husbands. Only one Table, Table 2, gives wife's age group. The relationship of wife's age group to her daily intake of green/yellow vegetables is not given, nor of wife's age group to husband's age group, husband's drinking habit or husband's occupational group.

Poisson Regression

The following gives the standard analysis of the tables published in Hirayama (1984). Since Tables 5, 7(1) and 9 are all collapsed versions of other Tables, they are omitted from

Exhibit 2

Form 2 **Second survey**

Health Questionnaire Name of Prefecture Health Center

District code	Household code	Individual code
Name	M / F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed
Address		
Place of birth	Prefecture City	Occupation (in detail)
For women	Number of children	Length of breast feeding after last delivery month(s) / Age at first marriage

Anamnesis

Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kizami (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2 Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure Others (1. Tea 2. Coffee 3. Cola 4. Cider)
Current Health Status (danger signals)		1. Stomach trouble, indigestion, no appetite, change in food choice. 2. Vaginal discharge, irregular bleeding. 3. Lump in the breast 4. Difficulty in swallowing. 5. Blood or mucos in stool. 6. Continued cough, bloody sputum, hoarseness. 7. Chronic ulcer in the mouth/skin. 8. Difficulty in urination, blood in urin. 9. Irritation/uneasiness 10. Difficulty in sleeping. 11. Heart trouble.
Currently		1. Healthy 2 In bed (by) from when.
Major illness during past 5 years		name of illness time duration. 1) 2)
Health Check		1 none 2 yes (stomach X ray chest X ray blood pression others)

analysis. Note that, because of different groupings of husband's occupational group, Table 3 cannot be derived from Table 8, nor Table 6 from Table 10. Indeed, since person years are not given, the study appears to call for a Proportional Mortality Analysis of lung cancer, other cancer and ischemic heart disease mortality in non-smoking wives, cross-classified by wife's age group (4) × husband's age group (4) × husband's smoking classification (5) × husband's drinking habit (4) × husband's occupational group (10) ×

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Exhibit 3

Tables as presented in Hirayama(1984)

TABLE	OUTCOME	FACTORS*
1	LCD	HAGE(4) x HCIG(5)
2	LCD[1]	WAGE(4) x HCIG(3)
3	LCD	HAGE(4) x HCIG(3) x HOCC(10)
4	LCD	HAGE(4) x HALC(4)
5	IHD[2]	HAGE(4) x HCIG(3)
6	IHD	HAGE(4) x HCIG(3) x HOCC(10)
7(1)	OTHCA[3]	HAGE(4) x HCIG(3)
7(2)	OTHCA	HAGE(4) x HCIG(3) x HOCC(10)
8	LCD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)
9	LCD	HAGE(4) x HCIG(2) x HOCC(2) x GYV(2)
10	IHD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)

1 LCD.......lung cancer deaths

2 heart disease deaths

3 cancer deaths

*Factors:

HAGE husband's age group

WAGE wife's age group

HCIG husband's daily smoking habit

HALC husband's daily alcohol intake

HOCC husband's occupational group

GYV wife's daily intake of green & yellow vegetables

Levels: In a factor XXX(n), n is the number of levels of factor XXX in the specified table

wife's daily intake of green/yellow vegetables (2). Parenthetically there is no reason today why, with modern computing techniques this basic tabulation should not have been analysed directly, instead of piecemeal as reported. Unfortunately the basic data is not available to the author (Hirayama, personal communication).

The analysis which follows is that recommended by Breslow & Day (1986) for cohort studies. In the absence of person years, the cumulative mortality rate over the period 1966–1981 is used as the response variate. (This assumes no "competing" causes of death and no loss to follow-up. This rate is not strictly a risk estimate since it depends on the duration of the study, the period of the study and on the choice of study population). A Poisson error structure is specified with a logarithmic link function which is the default for a Poisson error structure in GLIM (Payne 1985). The regressions are weighted according to the number of non-smoking wives in each cell.

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Following Breslow (1987), nuisance variables, irrespective of their technical significance, are fitted before the factor of interest, i.e. either husband's smoking status or green and yellow vegetable intake. A factor is considered to have a significant association with the specified mortality rate only if the deviance reduction in the model, for the degrees of freedom associated with fitting that factor, is significant at the 5% level. (Note that Dr. Hirayama here uses a one-sided 10% level of significance which is equivalent to a two sided test at 20% significance). Analysis of residuals and regression diagnostics are not given here. Rather the model fit is evaluated using the approximation of the residual deviance and its degrees of freedom to the χ^2 distribution which "may overstate the degree of departure from the fitted model when many cells contain small counts" (Breslow & Day 1986, p. 137).

Husband's Age Group, Husband's Drinking Habit and Lung Cancer Mortality

Age at interview is clearly a powerful factor which must be fitted first. In some tables age exhibits a powerful linear trend and can be fitted as a single numeric variable. Where this is possible it is done to achieve the most parsimonious model.

Table 4 gives a cross classification of husband's age group × husband's drinking habit for lung cancer mortality in non-smoking wives. It is surprising that other "nuisance factors" are not included. Nevertheless, this table is analysed first, largely to investigate the association of lung cancer mortality with husband's age group.

Standard Poisson regression of Table 4 confirms that husband's age group is an important factor in lung cancer mortality (see Exhibit 4). Husband's age group exhibits a strong linear trend with lung cancer mortality. A log-log plot of lung cancer mortality rate vs husband's age group however gives a slope less than 3 whereas a slope of 4 has been reported for non-smokers using attained age (Seidman 1985). Husband's drinking habit shows no significant association in this table with lung cancer mortality but no adjustment has been made for other nuisance variables. Thus one would expect an association between husband's drinking and smoking habits.

ETS and Lung Cancer Mortality (Tables 1, 2, 3)

The only measure of ETS exposure given is husband's smoking classification, the number of cigarettes reported in 1965 as smoked daily by the husband. The standard practice of demonstrating that a factor is significant before looking for a trend is followed here. As for husband's age group in Table 4 above, husband's smoking classification shows a strong linear trend in certain tables and is entered as a single numeric variable in the interests of parsimony where possible.

"Typical practice is to consider 5 year intervals of age and time so as to be able to study variation in rates" (Breslow & Day 1980, p. 47–48). Hirayama (1984) uses 10 year age groups and does not divide the 16 year period. In general, an age classification of 10 years at entry in a study lasting 16 years with no time dependent factors may mean that the age effect has been incompletely adjusted (Mantel 1983). Thus, for a lung cancer mortality rate which rises exponentially with age, it is plausible that the significance of husband's smoking classification is an indication of incomplete age adjustment, given the rapidly changing habits of cigarette smoking in the period before 1966 (Kristen 1986).

Note also that duration of ETS exposure is confounded to an unknown extent with age at first interview. Thus, in the absence of other information, assume a constant age at

Exhibit 4

Summary of the fit of the best† multiplicative model

OUTCOME TABLE	PREDICTIVE MODEL	DEVIANCE(d.f.)
LCD 1	A	13.0 (18)
	A+HCIG	3.7 (14)
LCD 2	WAGE	16.8 (8)
	WAGE+HCIG	10.7 (6)
LCD 3	A+HOCC+C	71.9 (108)
LCD 4	A	15.3 (14)
IHD 6	HAGE+HOCC	115.1 (106)
	HAGE+HOCC+HCIG	109.6 (104)
OTHCA 7(2)	HAGE+HOCC	134.7 (106)
LCD 8	A+HOCC+C	50.8 (44)
IHD 10	HAGE+HOCC+HCIG	50.7 (41)

Key:

A is husband's age fitted as a linear trend

C is husband's daily smoking habit fitted as a linear trend

other factors, outcomes as defined in Exhibit 3

†Best in the sense of minimum residual deviance after fitting all 'nuisance' parameters as factors or (if warranted) as trends and then fitting the explanatory variables, HCIG [Tables 1, 2, 3, 4, 7(1)] or GYV [Tables 8, 10]

marriage and at starting smoking. In 1965, older non-smoking wives of smoking husbands will have been exposed to ETS for a longer period than younger wives. (This expectation of an increased relative risk for older wives is not evident from an analysis of Table 2 (see Exhibit 7)). Form 1 (Exhibit 1) records the age at which the husband started smoking. Given this and the date of the marriage from a linked wedding certificate, it should be possible to estimate the duration of ETS exposure by the non-smoking wife of a smoking husband prior to 1966 as well as the wife's age at first exposure.

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Table 1, like Table 4, gives the cross-classification of husband's age group × husband's smoking status. As shown in Exhibit 4, only husband's age group is significant and exhibits a strong trend, as in Table 4. Although husband's smoking classification is not significant, it approaches significance ($\chi^2 = 9.3$ on 4 degrees of freedom, P just greater than 5%).

The effect of re-classifying husband's smoking classification from 5 levels to 3 levels can be seen in Table 3 which also gives a breakdown by 10 occupational groups, HOCC (10). Although husband's occupational group with 9 degrees of freedom is not significant, husband's smoking classification with 3 levels now is. Indeed husband's smoking classification with three levels now exhibits a strong trend (Exhibit 4).

Table 2 is unique in this publication in that lung cancer mortality is adjusted for wife's age group. Indeed this appears to be the only occasion on which Hirayama has included wife's age group in an analysis in any of his many publications from this study. (We shall see that husband's age group is not a surrogate for wife's age group.)

Standard Poisson regression of Table 2 as presented shows (Exhibit 4) that wife's age group, while a significant factor, does not exhibit a trend against lung cancer mortality. Again husband's smoking classification is on the borderline of statistical significance as judged by the change in the deviance ($\chi^2 = 6.1$ on 2 degrees of freedom). Clearly the evidence for a significant relationship between lung cancer mortality and husband's smoking classification is ambivalent even without considering the influence of non-sampling errors and confounding factors.

ETS and Ischemic Heart Disease (Tables 5, 6)

The consideration of multiple outcomes for associations with ETS indicates the multivariate nature of the analysis and the lack of prior hypotheses in this study. One should allow for multiple or repeated tests of significance in the evaluation of these results.

Table 6 gives a tabulation of ischemic heart disease mortality by husband's age group, husband's smoking classification and husband's occupational group. After adjustments for both husband's age group and husband's occupational group are made (Exhibit 4), husband's smoking classification is just non-significant by the established criteria ($\chi^2 = 5.6$ on 2 degrees of freedom). This is in contrast to Table 5 (not shown) which is Table 6 collapsed over husband's occupational group, showing some confounding between husband's occupational group and husband's smoking classification for ischemic heart disease.

ETS and Other Cancers

Table 7(2) classifies other cancer against husband's age group, husband's smoking classification and husband's occupational group, the same classification as for lung cancer mortality (Table 3) and for ischemic heart disease (Table 6). This again points out that a Proportional Mortality Analysis is the preferred method of analysis here. A univariate log linear analysis confirms that husband's occupational group is significantly associated with other cancer mortality. This association is almost entirely due to husband's occupational group 5, "farmers, laborers and fishermen" which has an estimated relative risk of 1.45 with 95% confidence limits of (1.04–2.03). No significant association with husband's smoking classification is detected with other cancer.

Green/Yellow Vegetables and Lung Cancer Mortality (Table 8)

Switching the focus now from husband's smoking classification to daily intake of green/yellow vegetables, we first fit all factors other than daily intake of green/yellow vegetables in Table 8 as nuisance parameters. The analysis of deviance reduction establishes that daily intake of green/yellow vegetables has a non-significant association (Exhibit 4).

Green/Yellow Vegetables and Ischemic Heart Disease (Table 10)

Table 10 gives ischemic heart disease mortality by husband's age group, husband's smoking classification, husband's occupational group and daily intake of green/yellow vegetables.

No significant association is found (Exhibit 4) with daily intake of green/yellow vegetables, after adjustment for these other factors ($\chi^2 = 0.6$ on 1 degrees of freedom).

In summary, standard Poisson regression, using the conventional 5% level of significance indicate, on the basis of these published tables,

- husband's smoking classification is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline significance and dependent on the presence or absence of other factors in the model and the number and grouping of classes used in the husband's smoking factor.
- that husband's drinking habit shows no significant association with lung cancer mortality in the limited data published here.
- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality or with ischemic heart disease mortality.
- that husband's smoking classification is of borderline significance with wife's ischemic heart disease mortality.
- that husband's smoking classification shows no significant association with other cancer mortality.

These findings may be compared against those of the original report. There Hirayama (1984) claims "a significantly increased risk of" lung cancer mortality "in relation to the extent of the husband's smoking ... The association was significant when observed by age of husbands ... and also by age of wives." "Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking was observed with ischemic heart disease when observed by husband's age group and husband's occupational group."

"The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking ... Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking."

Power Fit

Exhibit 4 which summarizes the best fitting multiplicative model indicates that in some instances this fit may not be too good (or that interaction terms are necessary). Thus, the residual deviance considered as an approximate χ^2 indicates that for both models fitted toTable 2, the fit is of borderline significance. This is true also of Table 7 (2), Table 8 and

Exhibit 5

Deviances (df) for additive, multiplicative and best fitting power models

OUTCOME TABLE	MODEL ADDITIVE	POWER	MULTIPLICATIVE
LCD Table 1	3.79 (12)	2.76 (12)	3.24 (12)
LCD Table 2	7.91 (6)	7.85 (6)	10.72 (6)
LCD Table 3	2.57 (6)	1.50 (6)	1.95 (6)
IHD Table 5	2.32 (6)	2.17 (6)	2.72 (6)
OTHER CA Table 7(1)	3.28 (6)	2.46 (6)	3.68 (6)

Model is 1+HAGE(4)+HCIG(5) for Table 1
.... 1+WAGE(4)+HCIG(3) for Table 2 and
.... 1+HAGE(4)+HCIG(3) for Tables 3, 5 and 7(1)

Rates are DTHS/POP (1966-1981)
for LCD (Tables 1,2,3), OTHER CA (Table 7(1)), IHD (Table 5)

Table 3 has been collapsed over HOCC

Table 10. This test is approximate. Nevertheless, it was decided to investigate the best fitting power model (Breslow 1986) to these tables. The goodness of fit of the additive, multiplicative and best fitting power model to these data are compared in Exhibit 5 in terms of residual deviance. Note that the additive and multiplicative models are special cases of the power model with exponents equivalent to one and zero respectively.

In Exhibit 5, an attempt has been made to fit the same predictive equation, adjusting for age and ETS exposure across the different sets given in Hirayama (1984). Overall, husband's age in 1965 classified by 10 year age groups, gives very satisfactory fits, irrespective of which Poisson model is used. In contrast, Exhibit 5 shows that poor fits result from the use of wife's age in 1965, classified in 10 year age groups, the multiplicative model giving the worst fit.

Exhibit 5 also reveals that the power-deviance curve is generally quite flat. Apart from Table 2, for which the additive model is the model of choice, the data, as presented in Hirayama (1984), do not discriminate well between additive and multiplicative models.

Exhibit 6

POWER VALUE FOR BEST MODEL

POWER

OUTCOME Table	ρ	$\hat{\rho}$	ρ
LCD Table 1	1	0.40	0
LCD Table 2	1	1.14	0
LCD Table 3	1	0.39	0
IHD Table 5	1	0.61	0
OTHER CA Table 7(1)	1	-	0

predictive equations as in Exhibit 5

- $\hat{\rho}$ meaningless since HC1G has zero estimates

The power value in the best fitting model is given in Exhibit 6. This lies between $\rho = 1$, the additive model and $\rho = 0$ (which is equivalent to the multiplicative model) for all but Table 2. The best fitting power model for Table 2 is larger than 1.00, indicating that the multiplicative model as fitted above, is contra-indicated. An additive model, then, is clearly preferred over the multiplicative model for Table 2, which, alone, uses wife's age group. However, the flatness of the deviance curve against ρ may indicate that the assumption of a Poisson error term is incorrect.

This finding may be interpreted in biological terms and in terms of information content. Although this study is considered to be one of the largest on ETS and lung cancer and contributes heavily to any meta-analysis estimate of passive-smoking effect (NRC report. 1986) it contains little information because of the absence of specific exposure, person year and time dependent data.

Wife's Age (Table 2)

Having shown that the additive model is the model of choice for Table 2, we now consider this analysis more fully. Unfortunately we are restricted to this one simple cross classification of wife's age group by husband's smoking classification using coarse intervals and omitting others factors. Under the additive model, wife's age group and husband's smoking classification are significant factors ($\chi^2 = 32.6$ on 3 degrees of

Exhibit 7

Table 2 Lung Cancer Relative Risk (1966–1981)

HUSBAND'S SMOKING

		Non	Ex or 1 – 19/d	20 + /d
WIFE'S AGE	40–49	1.0	2.4	3.3
	50–59	1.0	1.6	1.9
	60–69	1.0	1.2	1.0
	70–79	1.0	0.1	0.5

freedom for wife's age group and 8.84 on 2 degrees of freedom for husband's smoking classification, $0.05 > P > 0.01$).

Although this is an improvement over the multiplicative model, the residual deviance is 7.91 on 6 degrees of freedom, indicating that this model may still not be good fit. Likewise the best fitting power model had residual deviance of 7.85 on 6 degrees of freedom – not a great improvement.

This is paradoxical. As we move from husband's age group to wife's age group (which should give a more direct relationship between age and lung cancer mortality) we, in fact, find continued evidence of an interaction between wife's age group and husband's smoking classification, irrespective of which model we use. It must be concluded that Table 2 contains insufficient detail in wife's age group and exposure to ETS or that other factors, not shown, are associated with lung cancer mortality in the non-smoker.

An alternative way of explaining why the multiplicative model is not the model of choice when wife's age is used is to examine the relative risks. The use of the multiplicative model assumes that the relative risk is constant with age. Exhibit 7 however demonstrates a clear trend in the relative risk which falls from values above 1 at young ages to values below 1 over 70. These trends arise because of the different effects of age in the three smoking status categories. Clearly (as may be seen from Exhibit 8 (figure)) the rates for the three smoking status categories are approximately equal at wife's age 60–69 but differ (in different directions) at other ages. Exhibit 9 compares average annual rate by wife's age (Table 2) with the same rate when classified by husband's age (Table 1) and both are compared with estimated Japanese rates for females. The rates for Table 1 and Table 2 are both uniformly lower than Japanese rates for women. Either wives have a much more favorable experience than all women or Hirayama's study subjects are unrepresentative of Japanese wives or both. In addition Exhibit 9 reveals an anomaly in Table 2 in that, unlike Japan or Table 1, the lung cancer death rates when classified by wife's age show no age trend from age group 50–59 to 60–69!

This suggests a serious misclassification of wife's age, wives who were 50–59 being recorded as 60–69 at the initial interview. Alternatively, and more likely, lung cancer deaths for wives aged 60–69 at initial interview are seriously under reported, giving a spuriously low average annual year lung cancer death rate of 18 per 100,000 as compared with a Japanese rate for all women of 39.

Turning now to an examination of the selected cohort, we look at the percentage distribution of husband's smoking status by wife's age. Exhibit 10 gives a 1965 cross-

Exhibit 8

Table 2 Wife's Lung Cancer Death Rate (logarithm) (1966–1981) by Husband's Smoking Status (1965)

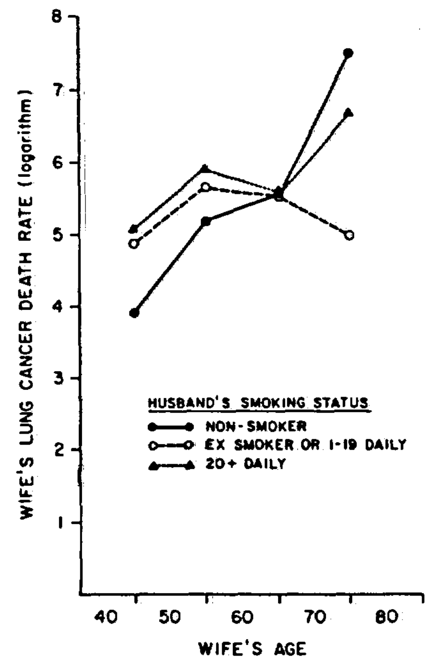

Exhibit 9

COMPARISON OF RATES BY AGE

Annual Average Lung Cancer Death Rate /100,000

1966–1981

AGE	JAPAN†	TABLE 1*	TABLE 2
40–49	12	7	8
50–59	20	12	18
60–69	39	23	18
70–79	46	36	35

† based on Japanese rates for women. (Segi et al., 1981)

* husband's age.

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Exhibit 10

Table 2 Distribution of Husband's smoking status by Wife's age

HUSBAND'S SMOKING

		Non	Ex or 1 – 19/d	20 + /d	Total
WIFE'S AGE	40–49	21%	46%	33%	38,025(100%)
	50–59	24%	49%	27%	32,089(100%)
	60–69	30%	51%	19%	20,344(100%)
	70–79	16%	62%	22%	1,082(100%)

Exhibit 11

Table 1 Distribution of husband's smoking status by his age

HUSBAND'S SMOKING

		Non	Ex	1 – 14/d	15 – 19/d	20 + /d	TOTAL
HIS AGE	40–49	19%	4%	27%	16%	34%	32,027(100%)
	50–59	23%	6%	29%	12%	30%	33,253(100%)
	60–69	29%	11%	30%	10%	19%	24,214(100%)
	70–79	37%	17%	30%	5%	11%	2,046(100%)

sectional view of cohort changes in husband's smoking habits. A number of points arise. Although Dr. Hirayama has published no information from his 3% re-interview survey on changes in smoking status between 1965 and 1971, such changes in smoking status occurred and may be of the order demonstrated in Exhibit 10 for husbands. (We have no information on wife's changes in smoking habits. Dr. Hirayama claims that 1.96% of the women polled in his 3% re-interview survey were misclassified as to smoking status. It is difficult to understand how he can discriminate between conversion from non-smoking to smoking status given the nature of the smoking question revealed in Exhibits 1 and 2. If 1.96% of wives were misclassified, what is the conversion rate from non-smokers to smokers in the period 1965–1971 among these wives?)

Secondly, the intermediate smoking classification (Ex or 1–19/d) is the most numerous of the three smoking status classifications for the husband and is a composite of ex-smokers and light and intermediate smokers (1–14/d and 15–19/d). It could be argued that as the most numerous the intermediate group should be used as the baseline for testing the significance above and below these rates for non-smokers and heavy smokers (20+/d) respectively. However, this group of wives has an unknown mixture of exposures to passive smoking. As indicated above, form 1 (see Exhibit 1) records

information on duration of exposure of a wife to her husband's smoking but this has never been used in Dr. Hirayama's many publications.

Finally, a husband's smoking status is clearly dependent on his age (Exhibit 11). Thus, as a surviving husband ages he is less likely to be classified as a 20+/d smoker and most likely to be classified as a non-smoker or ex-smoker. Dr. Hirayama groups ex-smokers with light smokers (what happens to "occasional smokers"? (see form 1 (Exhibit 1)). In terms of exposure before 1966 this is correct but it may be argued that ex-smokers should be grouped with non-smokers since wife's exposure is zero after 1965 and lung cancer latency is of the order of 10 years.

Better still, fine detail should be preserved in order to allow for the true expression of factors and covariates. Thus it is likely that the association of husband's smoking status with wife's lung cancer mortality is simply an example of incomplete age adjustment, using 10 year age groups with a 16 year cumulative mortality. In other words, husband's smoking status is confounded with wife's age. Again this can be remedied by using modern analytical techniques to analyse the data in detail.

Discussion

Dr. Hirayama's publications, over the years, have analyzed this longitudinal record linkage study from many aspects. Given the nature of the study and the absence of specific details, it is clear that these data can not be used to confirm hypotheses or to strengthen the evidence for or against a causal mechanism between causes of death (his outcomes) and his factors, since "we can be easily misled by variables not represented or recognized in a study" (Tukey & Mosteller 1977, p. 119) and since "tests of significance and confidence intervals that fail to account for the lack of fit of a given model may be seriously misleading" (Breslow 1987, p. 37).

The absence of relevant factors and specific details is shown here in the inability of these published data to discriminate between additive and multiplicative Poisson regression models. It is unfortunate that the Committee on Passive Smoking (NRC 1986) gave so much weight to Dr. Hirayama's conclusions in their review of the evidence for and against passive smoking as a cause of lung cancer.

This standard re-analysis of Hirayama (1984) points to husband's smoking status being a surrogate for some other factor or factors. Thus, an unadjusted analysis of husband's alcohol intake showed no association with lung cancer mortality. If husband's smoking status were a causal factor in the formation of lung cancer, one would expect alcohol intake also to be associated with this risk because of the association of smoking and drinking habits.

Comparison with other cohort studies shows how approximate the evaluation of ETS exposure is in this study. Thus, for example, Smith & Doll (1982), investigating the effect of irradiation on leukemia mortality use both age at first exposure and duration since first exposure as factors. Dr. Hirayama has linked his initial interview file with death certificates for selected causes of death. It should be possible to link wedding, divorce and death certificates (for all causes) to the original file in order to estimate the duration of the marriage. Further, since the age at which the husband started smoking was recorded, the duration of the wife's exposure to passive smoking could be estimated. This assumes that no non-smoking wife started smoking in the interval 1966–1981. Figure 1 of Hirayama (1984) and Kristen (1986) show a rapid rise in per capita cigarette consumption in this period in Japan. In the light of this increase, it is plausible to assume that a number of these wives became smokers after 1965. More non-smoking wives of smoking husbands

would be expected to become smokers than among those married to non-smokers because of the husband's example. Likewise, more wives of smokers are likely to have been misclassified as non-smokers in 1965 than wives of non-smokers (Lee, in press).

In the absence of information on duration of exposure, we know only the reported smoking status of husband and wife at initial interview. Assuming stability throughout, older wives in 1965 have been exposed for longer than younger wives. If so, relative risks should increase but the opposite is true (Exhibit 7). Indeed, as has been indicated, wife's age in 1965, is a less effective explanatory variable for cumulative lung cancer mortality than husband's age. Dr. Hirayama's analyses which use the spouse's age for age standardization are of questionable value. Theories of carcinogenesis relate the incidence of cancer to the age of the experimental animal or the individual. The analytical comparisons given here indicate that husband's age *cannot* be used as a surrogate for wife's age if the age at entry of the decedent is used. The importance of this conclusion may be seen in the observation that, if Dr. Hirayama's study is excluded from a global estimate of passive smoking effects on lung cancer, the resultant meta-analysis gives a value which is not significantly greater than 1!

Dr. Hirayama's study ascertained 142,857 women 40 years or over in 1965. Figures 7 and 8 of Hirayama (1984) document the smoking history or exposure of 108,906 females, leaving 33,951 women unaccounted for. It might be assumed that 24% of the female cohort were widows in 1965 except for Dr. Hirayama's statement "information on the smoking history of the husbands of non-smoking women with lung cancer was available - in 77.3% of cases (174 out of 240)" (Hirayama 1981). This means that the 91,540 wives analysed here and in Hirayama (1984) represent 77.3% of a total of 118,422 wives in 1965. Clearly it is impossible to re-construct the total female cohort from the information given. If, as stated by Dr. Hirayama, 23% of his study group are missing, then his confidence limits are too narrow in that they do not allow for the effect of these non-sampling errors. Inclusion of non-sampling errors for the 23% missing wives totally negate his claims of significance for the association between passive smoking and lung cancer and between green and yellow vegetable intake and lung cancer.

This investigation prompts the author to call for an international panel of scientists to be given access to Dr. Hirayama's files. An independent evaluation is needed of the contribution which this unique study can make to the role of passive smoking and dietary habits in the etiology of lung cancer and heart disease.

Acknowledgement: The author is indebted to Dr. John Viren for his suggestions, criticisms and advice.

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clearly inadequate for the purposes at hand. Rather fine categorisation is used for husband's occupation, but analysis of the data does not indicate that this is a significant predictor. The stratification for age, on the other hand, is far too coarse. Variations of cancer incidence within 10-year age ranges are large compared with the variations attributed to the husband's smoking. Even relatively small differences in the age distribution of the three populations could thus produce the reported apparent effect. The use of husbands' rather than wives' ages for stratification compounds the problem.

The measure of risk is also inappropriate for a study of such extended duration. The number of person years at risk rather than the number of subjects should be used as the exposure variable, since many subjects would have died of other causes during the study. The appropriate procedure for analysing data of this type is given in Mantel's original paper.[1]

Finally, it is clear from the original paper that Dr Hirayama analysed several causes of death, but reported statistics only for lung cancer. The procedure of reporting only the most significant result from a choice of several possible dependent measures a posteriori is a common error which naturally leads to inflated estimates of significance. Only an appropriate multivariate test can properly estimate statistical significance in this situation.

The analysis reported must thus be regarded as inconclusive unless more refined analyses are able to confirm the results. We endorse the author's suggestion that further study based on larger samples is needed, but we emphasise that such studies can be useful only if the relevant biomedical data are recorded and analysed in sufficient detail to isolate the hypothesised effect from confounding factors.

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[1] Mantel N, Halperin M. *Journal of the American Statistical Association* 1963;58:611-27.

SIR,—Most of the questions raised in my letter (3 October, p 917) were not addressed in the response of Dr Hirayama that followed. The first readings of his original paper troubled me in view of his recognised work, so that before I commented I reviewed every Hirayama paper in the literature on this study population to see if the collective information might answer the questions. A map of Japan was constructed by prefectures and minor population subdivisions and the areas of the study were marked as nearly as they could be ascertained. Review of the reports on the epidemiology and clinical aspects of lung cancer of other Japanese scientists and finally a serious study of Japanese demography, industry, disease trends, and all pertinent data were made; so the questions asked were serious and responsible.

Dr Hirayama did not answer the question about how or why the specific health stations surveyed were selected, or how the few prefectures of the total in Japan from which the health stations were chosen were selected. He admitted that the selection was not random and states, "The satisfactory representativeness of the sample was confirmed after the survey." He does not say by what criteria this was confirmed.

Mapping of the areas selected for study and of the industrial concentrations shows them to be related in nearly every instance. Dr Hirayama states, "Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample." Asbestos and other industrial exposures would have to be considered according to the locations of the study areas and of the industrial complexes as revealed on the map of Japan. The areas were nearly all in the areas with high standardised mortality ratios in the excellent and fully documented countrywide epidemiological lung cancer mortality study of Minowa *et al*.[1] The tabulation on the basis of the husbands' ages is not explained. According to the median age at time of marriage in Japan, there is a difference between husbands' and wives' ages, the wives being generally younger. Dr Hirayama states, "We have tables by wives' ages separately." They were not found in the literature search on these data.

No response at all was made to the following questions: (1) Were the families whose medical care was covered by industry omitted from the study? (2) To what population is Hirayama referring? (3) Why were 31% of the women surveyed (and 40% of the women smokers) listed as unknown or not specified as to occupation? For a person to person survey, this suggests methodological problems. (4) Why were references to current Japanese studies by reputable men, Minowa *et al*[1] and Aoki,[2] whose findings did "not seem to explain the prefectural differences of lung cancer mortality" not mentioned? (5) The report by Ishikawa[3] on the preponderance of adenocarcinoma in Japan, in a footnote of which he acknowledges the assistance of Dr Hirayama, his colleague as a reviewer, is not referred to in the answer, although this is very important to this discussion.

Two new issues were introduced by Dr Hirayama in his response, one on the quantity of sidestream smoke inhaled by the wives, without any discussion of the quantity smoked in houses or in the presence of the wives. All the sidestream smoke of husbands' cigarettes would not be inhaled. A remarkably careful study on this subject was reported in 1978 by a French group that helps to explain the differences reported by different techniques of measurement. They improved and explained each innovation they used to overcome logistical problems noted in previous studies. They concluded, with valid proof, that on the strictly toxicological level there is no hazard for non-smokers. The report does not neglect to remark on the problems that are presented to a very important fraction of the population, however. The second issue introduced in the reply was that inhalation through the nose is different from the smoker's direct inhalation. This did not consider the superb filtering system, which would conceivably reduce the amount of ambient smoke inhaled by the wives.[4]

Finally, the far-reaching implications of this unproved passive smoking effect are already in evidence in the literature.

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[1] Minowa M, Shigematsu I, Nagai M, Fukutomi K. *Soc Sci Med* 1981;15D(1):225-31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541-50.
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SIR,—Dr T Hirayama (17 January, p 183) reports a greater risk of lung cancer in non-smoking women when their husbands smoke than when they do not. Assessing the statistical significance of this association by a χ^2 trend statistic on one degree of freedom, Dr N Mantel (3 October, p 914) showed that a non-significant value of 3·31 is obtained if age and occupation are ignored. However, if these factors are taken into account, on the basis of data given in table I of Dr Hirayama's recent letter (3 October, p 916), a higher χ^2 value of 8·70 is obtained, which is statistically significant ($p<0·01$), and similar to, though not identical with, to the value of 10·88 given in his original paper. While this slight discrepancy might have been due, perhaps, to the use of narrower age bands in Dr Hirayama's original calculations, it is clear that the much more significant differences claimed in tables II and III of his letter are due to a statistical error.

Table II, which gives a very much higher χ^2 value of 36·81 for a similar comparison, is based on the false assumption that the lung cancer rate of non-smoking women with husbands who did not smoke is known precisely. The correct calculation, given in my table, gives a much lower level of significance for the Japanese data, and his calculations for the American[1] and Greek[2] data are similarly in error. Consideration only of women with smoking husbands has also led Dr Hirayama to conclude incorrectly that the American study was materially less powerful than the Japanese study because of sample size. In fact, the studies were of very similar power, a slightly smaller total number of deaths in the American study (153 compared with 174) being balanced by the greater stability of the denominator in the relative risk calculations, due to the greater number of deaths in women whose husbands did not smoke (65 compared with 32).

The source of the error in his table III is not clear, but the remarkably narrow 95% confidence bands for relative risk given in the table below the figure cannot be even approximately correct. How, for example, can the ratio of 2·94 given for the comparison of lung cancer rates between non-smoking men whose wives smoke (seven deaths out of 1010) and non-smoking men whose wives do not smoke (50 deaths out of 19 279) possibly have 95% limits as close together as 2·65 and 3·26—that is, $\pm 10\%$—when the 95% limits for the seven observed deaths are approximately 2 and 12—that is, $\pm 70\%$—and the variability of the relative risk must be greater than this?

Hugod *et al*[3] have shown that under quite extreme passive smoke conditions, sufficient to produce a carbon monoxide air concentration of 20 parts per million, a non-smoker would take 11

Observed and expected deaths from lung cancer in non-smoking women in the Japanese study according to the smoking habit of their husbands

	Husbands do not smoke		Husbands smoke			
	Observed	Expected	Observed	Expected	χ^2	p
As given by Hirayama	32	(32·0)	142	85·8	36·81	<0·00001
Correct calculation	32	45·8*	142	128·2*	5·78	<0·05

* Standardised for age and occupation on the basis of data in table I of Dr Hirayama's letter (3 October, p 916).

hours to take in an amount of tar equivalent to that inhaled by the smoker of an average cigarette and 50 hours to take in the equivalent amount of nicotine. Similar estimates can be made from other studies,[1-4] suggesting that *in terms of dose* one passively smoked cigarette is equivalent to a very small fraction of one actively smoked cigarette. In Dr Hirayama's study, on the other hand, elevations of lung cancer risk in active smokers of about five cigarettes a day are similar to those seen in non-smoking women married to smokers of 20 or more cigarettes a day. As these husbands are stated to smoke only 8·4 cigarettes a day at home and these presumably not all in the presence of the wife, his results are implicitly suggesting that *in terms of lung cancer response*, one actively smoked cigarette and one passively smoked cigarette are virtually equivalent.

This contrast is so striking that one must seriously doubt whether the elevated lung cancer risk seen in non-smoking wives of smokers, statistically significant as it may be, is really caused by the passive smoke exposure. It seems far more likely that the explanation lies in some hitherto undiscovered confounding or biasing factor.

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[1] Garfinkel L. *J Nat Cancer Inst* 1981;66:1061-6.
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[6] Russell MAH, Feyerabend C. *Lancet* 1975;i:179-81.

**We sent this letter to Dr Hirayama, who replies below.—ED, *BMJ*.

SIR,—Since in Garfinkel's paper the only data available were expected frequencies based on the risk for women with non-smoking husbands, similar calculations were attempted with the Japanese and Greek data and presented in table II. If Garfinkel had shown the complete data better comparison could have been made, as suggested by Mr Lee.

Mr Lee also worries about the data as they suggest that the risk of passive smoking is almost equivalent to that of light smoking. The only way to answer such questions must be by carrying out in-depth studies of the chronic toxicity of sidestream smoke and of health consequences resulting from prolonged exposure to passive smoking. The study by White and Froeb suggests a considerable effect on the airways from passive smoking.[1]

I regret that errors have been found in the 95% confidence intervals shown in the figure in my last letter. The correct values are given in the accompanying figure. The errors do not, however, influence the substance of my letter.

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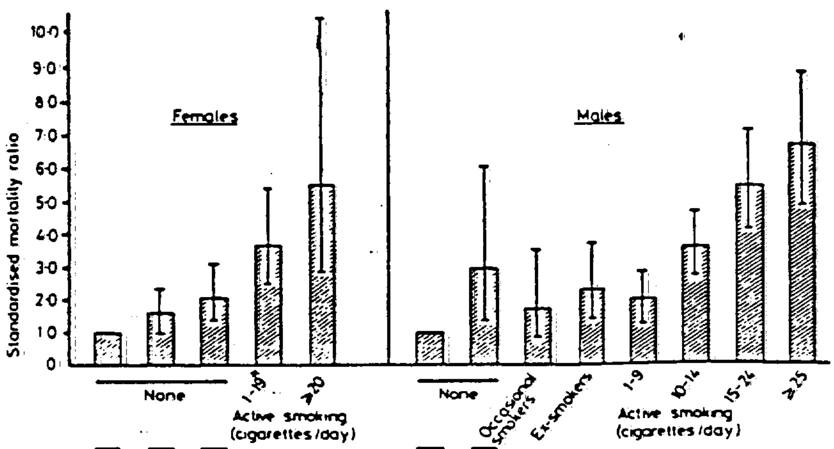
[1] White JR, Froeb HB. *N Engl J Med* 1980;302:720-3.



	Husband's smoking habit: None	1-19	≥20			Wife's smoking habit: None	Daily*						
No of deaths:	32	86	56	79	8	50	7	9	27	57	246	150	87
Population:	21895	44184	25461	16080	1286	19279	1010	1991	4185	9603	27127	14335	6280
95% confidence interval: Upper		2·39	3·11	5·32	10·29		6·08	3·52	3·69	2·91	4·70	7·20	8·88
RR		1·61	2·08	3·64	5·51		2·94	1·74	2·31	1·98	3·53	5·46	6·63
Lower		1·09	1·39	2·49	2·95		1·42	0·86	1·45	1·35	2·65	4·14	4·95

*Including occasional smokers and ex-smokers

Active and passive smoking and standardised mortality rates for lung cancer: relative risks (RR) with 95% confidence intervals—prospective study, 1966-79, Japan. (Revised version of figure published 3 October, p 917.)

Diseases of modern civilisation

SIR,—Certainly we can all agree with the Revd H C Trowell and Dr D P Burkitt (7 November, p 1266) that there are several conditions that are uncommon in developing countries but have become increasingly common in the West. They add that in their book *Western Diseases: Their Emergence and Prevention* "there is little hard evidence that would warrant a recommendation for dietary change in these countries."

There is, however, a great deal of evidence, from experiments with laboratory animals and with human subjects, that one item in Western diets, in the quantities now commonly being consumed, produces a range of abnormalities that indicate its likely involvement in producing some of the Western diseases (references given in a recent paper[1]). Here is an abbreviated list: increased concentration of cholesterol and triglyceride, decreased concentration of high-density lipoprotein cholesterol, increased concentration of insulin and corticosteroids, and increased concentration of uric acid in the blood; impaired glucose tolerance; diminished tissue sensitivity to insulin; increased adhesiveness and aggregation of blood platelets; paradoxical electrophoretic behaviour of blood platelets; retinopathy; nephropathy indistinguishable both histologically and biochemically from that seen in diabetes mellitus. It is difficult to imagine that more evidence is needed to indict sugar as a likely cause of at least two of the "Western diseases," coronary heart disease and diabetes.

The average consumption of sugar is now about 1 kg a week in Western countries, 25 times what it was before the industrial revolution. Some people take two or three times this average. I see no problem about what should be the most sensible dietary recommendation we could be making.

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[1] Yudkin J. *Am J Clin Nutr* 1981;34:1453.

Alcohol and alcoholism

SIR,—Dr Richard Smith's series of papers on alcoholism (26 September, p 835; 3 October, p 895; 10 October, p 972; 17 October, p 1043; 24 October, p 1108; 31 October, p 1170, and 7 November, p 1251) was timely and generally accurate and comprehensive, but I was surprised to see no reference to supervised disulfiram—one treatment which does seem to be of specific benefit in alcoholism. This has been shown in three well-designed controlled trials and there are no contrary findings. All the studies stress that supervised disulfiram is an extension of the therapeutic relationship and not a substitute for it.

Gerrein *et al*[1] found that 85% of patients given disulfiram twice weekly under supervision remained in treatment, compared with a maximum of 39% in patients who had once-weekly supervised disulfiram or unsupervised disulfiram treatment. The figures for those abstaining for a minimum of eight weeks were 40% compared with a maximum of 15%. Azrin[2] reported that for patients given the same intensive community-based psychotherapeutic and rehabilitative programme, those in whom the administration of disulfiram was supervised—usually by their wife—did vastly better than those on unsupervised medication. Drinking days were 2% for the supervised group against 55% for the unsupervised. Unemployment was 20% against 56%; and time spent in institutions was nil against 45%. This last figure has obvious financial implications. In an employee treatment programme, Robichaud *et al*[3] found that absenteeism averaged 9·8% before treatment, 1·7% during treatment with twice-weekly supervised disulfiram given by the factory nurse, and 6·7% when treatment was discontinued. All these studies used a standard dose of disulfiram, which was probably inadequate for some patients, and no alcohol challenge was done.

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hours to take in an amount of tar equivalent to that inhaled by the smoker of an average cigarette and 50 hours to take in the equivalent amount of nicotine. Similar estimates can be made from other studies,[4-6] suggesting that *in terms of dose* one passively smoked cigarette is equivalent to a very small fraction of one actively smoked cigarette. In Dr Hirayama's study, on the other hand, elevations of lung cancer risk in active smokers of about five cigarettes a day are similar to those seen in non-smoking women married to smokers of 20 or more cigarettes a day. As these husbands are stated to smoke only 8·4 cigarettes a day at home and these presumably not all in the presence of the wife, his results are implicitly suggesting that *in terms of lung cancer response*, one actively smoked cigarette and one passively smoked cigarette are virtually equivalent.

This contrast is so striking that one must seriously doubt whether the elevated lung cancer risk seen in non-smoking wives of smokers, statistically significant as it may be, is really caused by the passive smoke exposure. It seems far more likely that the explanation lies in some hitherto undiscovered confounding or biasing factor.

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[1] Garfinkel L. *J Nat Cancer Inst* 1981;66:1061-6.
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**We sent this letter to Dr Hirayama, who replies below.—ED, *BMJ*.

SIR,—Since in Garfinkel's paper the only data available were expected frequencies based on the risk for women with non-smoking husbands, similar calculations were attempted with the Japanese and Greek data and presented in table II. If Garfinkel had shown the complete data better comparison could have been made, as suggested by Mr Lee.

Mr Lee also worries about the data as they suggest that the risk of passive smoking is almost equivalent to that of light smoking. The only way to answer such questions must be by carrying out in-depth studies of the chronic toxicity of sidestream smoke and of health consequences resulting from prolonged exposure to passive smoking. The study by White and Froeb suggests a considerable effect on the airways from passive smoking.[1]

I regret that errors have been found in the 95% confidence intervals shown in the figure in my last letter. The correct values are given in the accompanying figure. The errors do not, however, influence the substance of my letter.

T HIRAYAMA

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[1] White JR, Froeb HB. *N Engl J Med* 1980;302:720-3.

Diseases of modern civilisation

SIR,—Certainly we can all agree with the Revd H C Trowell and Dr D P Burkitt (7 November, p 1266) that there are several conditions that are uncommon in developing countries but have become increasingly common in the West. They add that in their book *Western Diseases: Their Emergence and Prevention* "there is little hard evidence that would warrant a recommendation for dietary change in these countries."

There is, however, a great deal of evidence, from experiments with laboratory animals and with human subjects, that one item in Western diets, in the quantities now commonly being consumed, produces a range of abnormalities that indicate its likely involvement in producing some of the Western diseases (references given in a recent paper[1]). Here is an abbreviated list: increased concentration of cholesterol and triglyceride, decreased concentration of high-density lipoprotein cholesterol, increased concentration of insulin and corticosteroids, and increased concentration of uric acid in the blood; impaired glucose tolerance; diminished tissue sensitivity to insulin; increased adhesiveness and aggregation of blood platelets; paradoxical electrophoretic behaviour of blood platelets; retinopathy; nephropathy indistinguishable both histologically and biochemically from that seen in diabetes mellitus. It is difficult to imagine that more evidence is needed to indict sugar as a likely cause of at least two of the "Western diseases," coronary heart disease and diabetes.

The average consumption of sugar is now about 1 kg a week in Western countries, 25 times what it was before the industrial revolution. Some people take two or three times this average. I see no problem about what should be the most sensible dietary recommendation we could be making.

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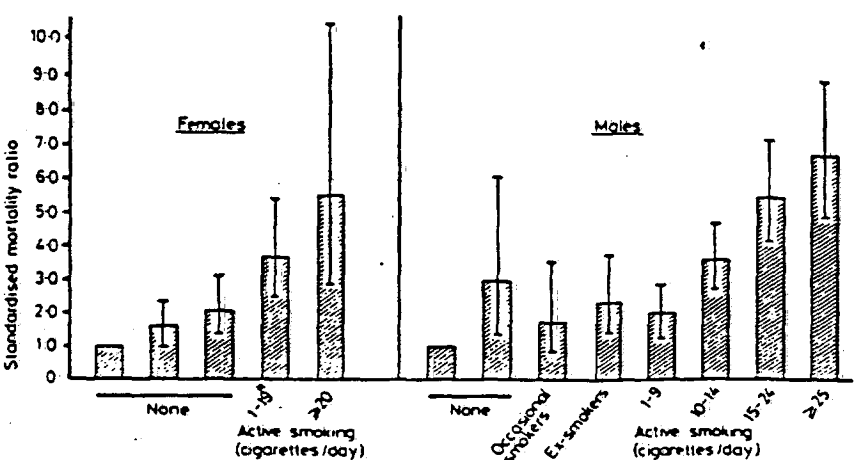
[1] Yudkin J. *Am J Clin Nutr* 1981;34:1453.

Alcohol and alcoholism

SIR,—Dr Richard Smith's series of papers on alcoholism (26 September, p 835; 3 October, p 895; 10 October, p 972; 17 October, p 1043; 24 October, p 1108; 31 October, p 1170, and 7 November, p 1251) was timely and generally accurate and comprehensive, but I was surprised to see no reference to supervised disulfiram—one treatment which does seem to be of specific benefit in alcoholism. This has been shown in three well-designed controlled trials and there are no contrary findings. All the studies stress that supervised disulfiram is an extension of the therapeutic relationship and not a substitute for it.

Gerrein *et al*[1] found that 85% of patients given disulfiram twice weekly under supervision remained in treatment, compared with a maximum of 39% in patients who had once-weekly supervised disulfiram or unsupervised disulfiram treatment. The figures for those abstaining for a minimum of eight weeks were 40% compared with a maximum of 15%. Azrin[2] reported that for patients given the same intensive community-based psychotherapeutic and rehabilitative programme, those in whom the administration of disulfiram was supervised—usually by their wife—did vastly better than those on unsupervised medication. Drinking days were 2% for the supervised group against 55% for the unsupervised. Unemployment was 20% against 56%; and time spent in institutions was nil against 45%. This last figure has obvious financial implications. In an employee treatment programme, Robichaud *et al*[3] found that absenteeism averaged 9·8% before treatment, 1·7% during treatment with twice-weekly supervised disulfiram given by the factory nurse, and 6·7% when treatment was discontinued. All these studies used a standard dose of disulfiram, which was probably inadequate for some patients, and no alcohol challenge was done.



	Females					Males							
Husband's smoking habit (females) / Wife's smoking habit (males):	None	1-19	≥20			None	Daily						
No of deaths:	32	86	56	79	8	50	7	9	27	57	246	150	87
Population:	21895	44184	25461	16080	1286	19279	1010	1991	4185	9603	27127	14335	6280
95% confidence interval: Upper		2·39	3·11	5·32	10·29		6·08	3·52	3·69	2·91	4·70	7·20	8·88
RR		1·61	2·08	3·64	5·51		2·94	1·74	2·31	1·98	3·53	5·46	6·63
Lower		1·09	1·39	2·49	2·95		1·42	0·86	1·45	1·35	2·65	4·14	4·95

*Including occasional smokers and ex-smokers

Active and passive smoking and standardised mortality rates for lung cancer: relative risks (RR) with 95% confidence intervals—prospective study, 1966-79, Japan. (Revised version of figure published 3 October, p 917.)

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PRESENT AND FUTURE OF INDOOR AIR QUALITY

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Present and future of indoor air quality
C.J. Bieva, Y. Courtois, M. Govaerts, editors

ASSESSING THE VALIDITY OF A JAPANESE COHORT STUDY

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INTRODUCTION

Results of a Japanese cohort study published by Takeshi Hirayama (3-6) have been influential in the assessment of cancer risks of non-smoking women exposed to environmental tobacco smoke (ETS) through their husbands' smoking. We compared mortality projections, based on Japanese national death rates, with the reported cohort mortality. These comparisons revealed serious external and internal inconsistencies in the study results:

* Reported cohort death rates were lower than those for all Japan, apparently because mortality tracing was incomplete and death rates among those lost to follow-up were higher than among those traced.
* Cohort mortality deficits varied greatly among sub-cohorts defined by entry age and marital status.

These inconsistencies raise the possibility that selection biases are present in the data which might distort comparisons between exposed and non-exposed groups.

COHORT SELECTION AND FOLLOW-UP

* The cohort was recruited in the last quarter of 1965 from 49 geographic areas within 29 Health Center Districts in 6 Japanese prefectures.
* Of persons aged 40-79 in the survey areas, 95% were included in the cohort (prefecture range: 91% to 99%). "Only those persons found healthy" were recruited. The criteria for exclusion on health grounds were not reported.
* The age distribution of the cohort was similar to that of the 1965 Japanese population, except that the cohort under-represented the 70-79 age group.
* The cohort was followed for 16 years to the end of 1981. The number of subjects lost to follow-up was not reported.

LIFE TABLE PROJECTIONS

Hirayama reported that age-specific mortality rates in the cohort, for all causes of death and for specific causes, were similar to those in the Japanese population. In fact, crude death rates for the 16-year study period, calculated by dividing reported total deaths by person-years of observation, were substantially lower than what would be expected from national death rates (Table I).

We arrived at this conclusion by constructing mortality projections for the

cohort, based on standard demographic life table procedures. Japanese death rate statistics were obtained from U.N. Demographic Yearbooks (7) for all-cause mortality, and from the Gann Monograph (2) for cancer mortality. The life tables provide year-by-year projections of cumulative deaths and person-years by age at observation. Cause-specific mortality projections were obtained by applying cancer death rates to the person-year projections. For smoking-specific sub-cohorts, adjustments to the published death rates were made by using the reported cohort mortality ratios for smokers versus non-smokers.

MORTALITY IN PERSONS LOST TO FOLLOW-UP

Total reported deaths in the cohort were 16,000 fewer than total projected deaths. For males, reported deaths were 8,600 (22.5%) less than projected, and for females reported deaths were 7,400 (25.5%) less than projected.

From the reported numbers of deaths, we calculated the numbers of person years which would have been observed in the cohort if there had been 100% follow-up. At the end of the 16-year study period, the totals of these calculated person-years were 108,000 more than reported person-years for males, and 95,000 more than reported for females. Those differences show that follow-up of the cohort must have been less than 100%. This conclusion is derived entirely from the reported cohort deaths and person-years of observation, and is not in any way based on the life table projections. Assuming that on the average 8 years of observation were lost per untraced person, an estimated 25,000 subjects, or about 10% of the whole cohort, were lost to follow-up.

The life table projections suggest that some 16,000 cohort deaths were not traced. That number is 64% of the estimated 25,000 persons lost to follow-up, as compared with approximately 21% of reported deaths among the cohort members who,

TABLE I

CRUDE DEATH RATES PER 100,000 PERSON-YEARS

	Males			Females		
	Projected Rate	Reported Rate	% of Projected	Projected Rate	Reported Rate	% of Projected
All Cause	2,300	1,824	79*	1,409	1,069	76
All-site Cancer	575.3	500.4	87	329.9	263.4	80
Lung Cancer	86.6	81.3	94	24.9	21.1	85

* Reported crude death rate as a percentage of projected.

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according to our estimates, were not lost to follow-up. This mortality differential is a possible explanation for the differences between reported and projected death rates noted above. In fact it is the most likely reason, since the alternative explanations discussed below seem inadequate to account for differences of the magnitude observed.

OTHER EXPLANATIONS FOR MORTALITY DEFICITS

We considered whether the discrepancy between reported cohort death rates and national rates could be explained by sampling variation, by lower death rates in the geographic areas represented in the cohort, or by "healthy person" effects.

* The size of the cohort is too large for sampling variation to be a credible explanation. For example, a 95% confidence interval for the ratio of reported to projected all-site cancer mortality among women is 78% to 82%.
* Japanese vital statistics by prefecture show regional variations in cause- and age-specific death rates, but these prefectural statistics do not suggest that death rates in the cohort as a whole would have been substantially lower than national rates. Thus it seems unlikely that regional variations could explain rate differentials of the magnitude indicated by the life table projections.
* Since there were some exclusions from the cohort on health grounds, one would expect an initial healthy person effect. However, examination of the ratios of reported deaths to life table projections in intervals of the 16-year study period shows that there were still very substantial cohort deficits in the last years of the study, and it is unlikely that a healthy person effect would persist strongly for so long in a cohort with entry ages of 40 to 79 years.

THE NON-SMOKING MARRIED WOMEN COHORT

At the beginning of the study period, the cohort contained 91,540 non-smoking married women (NSMW). A total of 16,181 deaths were projected for the NSMW, and 9,106 were reported. For all-causes, all-site cancer, and lung cancer, the percentages of reported to projected mortality for the NSMW were 56%, 67%, and 72% respectively. The remarkable feature of these projections is that while the mortality deficits relative to projections are very large for the NSMW (44%, 33%, and 28% for all-causes, all-site cancer, and lung cancer respectively), they are quite small for all other women (3%, 6%, and 3% respectively).

To investigate whether this pattern could be due to marital mortality differentials, we constructed a life table based on 1975 Japanese marital status-specific death rates (2). The result of our analysis was that reported total deaths were 63% of projected for the NSMW sub-cohort, while the ratio for all other women was 96%. Thus it appears that marital mortality differentials can explain only a

small part of the differences between the NSMW and other women in the reported versus projected mortality deficits.

When we compared reported and projected lung cancer mortality for the NSMW by entry-age decade, another internal inconsistency became apparent. Reported lung cancer mortality was only 51% of projected for the 60-69 entry-age group, while for younger women (40-59 years at entry) reported mortality was 84% of projected.

CONCLUSIONS

In their monograph on the design and analysis of cohort studies, Breslow and Day (1) note that: "The validity of a cohort study depends fundamentally on complete ascertainment of the events of interest (e.g., cancer death) ... ." Our analyses strongly suggest that reported death rates in the Hirayama cohort were substantially lower than Japanese national rates because mortality among persons lost to follow-up was higher than among those successfully traced. If this explanation is correct, it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality. Such biases could arise, for example, if there were more complete ascertainment of vital status among those exposed than among those not exposed. The striking internal inconsistencies described above, between sub-cohorts defined by marital status and entry age, reinforce these doubts about the validity of the study.

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taking and is unpleasant to the patient, if not dangerous; and, secondly, the desire of the clinician to have some x-ray plates to look at and interpret in addition to the radiologist's report, rather than having to rely entirely on the endoscopist. One can understand the second reason, especially where the clinician is keen to be closely associated with his patient's investigations wherever possible; but I do not think it is a good reason. As for the first, I think this reflects the fact that so many endoscopies are carried out without adequate supervision by senior or well-trained clinicians, which may result in a poor diagnostic yield, unreliability, and—what is probably an even more important factor in militating against the use of endoscopy as a primary procedure—considerable discomfort and even distress to the patient. Where endoscopy services are properly organised and the examinations are carried out only by fully committed specialists or specialists in training, these objections should not apply. After all, we do not expect our registrars or ourselves to wander into an x-ray department and carry out the occasional barium meal.

I would therefore disagree with your opinion strongly and suggest that in the not-too-far-distant future an endoscopy will be widely regarded as the investigation of first choice in patients with any form of upper gastrointestinal symptom.

J S KIRKHAM

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Non-smoking wives of heavy smokers have a higher risk of lung cancer

SIR,—Dr Takeshi Hirayama (17 January, p 183) states that there is an increased lung cancer risk in non-smoking Japanese women married to heavy smokers. If his results were to be interpreted in favour of a positive relationship between passive smoking and lung cancer, considerable implications might be drawn for health policies in general. In our opinion, his documentation and conclusions invite critical comment for several reasons.

The study is hampered by certain inadequacies. There is no definition of histological types in the lung cancers recorded in these women. For quite some time—at least since the paper of Wynder *et al*[1]—female lung cancer has been known to include a high proportion of adenocarcinomas and alveolar cell carcinomas. Moreover, Dr Hirayama's study fails to explain a lung cancer mortality rate of 18/100 000 in unmarried non-smoking women with reference to the fact that the 101 unmarried women dying of lung cancer were likely to have been recruited from smokers and non-smokers in the same proportion as their married compatriots. However, in the non-smoking wives of smokers the respective mortality rate is only 14·6/100 000. The proffered argument that unmarried women are more likely to be smokers than married ones could support the first assumption only if more than 50% of all unmarried women were actually smokers. This is highly improbable since the author admits that not more than 15% of Japanese women smoke at all.

Surprisingly, the study maintains that the non-smoking wives of heavy smokers are more likely to get lung cancer in rural than in urban parts of Japan, thereby disagreeing with the results of other studies from various countries. In Germany Ulmer[2] found that from 1971 to 1975 women living in an urban district died of bronchial carcinoma 2·19 times more often than those in a comparable rural district. None of the recent studies on passive smoking has asserted a correlation between passive smoking and the development of lung cancer[3-6] except for a paper by Trichopoulos *et al*,[7] whose small number of inappropriately selected cases appears unable to yield convincing results. One well-known effect of passive smoking is the irritation of eyes, nose, and throat which may even lead to reduced maximal pulmonary function; another is the impairment of powers of concentration felt by non-smokers dwelling in smoke-infested rooms.[8-10]

A dose-effect relationship in the development of malignancy is undisputed. Passive smokers living and working in smoke-infested rooms will take up smoke mainly through the nose (like pipe smokers), using the natural filter that smokers evade. (This explains the fact that the lung cancer rate is not raised among non-inhaling pipe smokers and cigar smokers.) The side-stream smoke, involuntarily taken up by the passive smoker, does still contain a high level of the noxious substances contained in tobacco, but they are diluted and weakened by normal room ventilation.[11] If we assume that the effect of 20 "passively smoked" cigarettes approximately equals that of one "active" (inhaled) cigarette, the carcinogenic substances diluted in this smoke would have to act at incredibly low concentrations to produce the alleged effect. In view of the dose-effect correlation this is highly improbable.

In view of so many open questions Dr Hirayama's conclusions do not appear very well founded. His paper, however, may stimulate further studies of greater statistical reliability.

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[1] Wynder EL, Covey LS, Mabuchi K. *J Nat Cancer Inst* 1973;51:391-401.
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SIR,—Dr Takeshi Hirayama's report (17 January, p 183) indicating that non-smoking Japanese wives of heavy smokers have an increased risk of lung cancer has far-reaching implications and needs to be seriously examined. In this regard the study apparently failed to consider the exposure of Japanese women to indoor air pollution from household heating and cooking equipment. Traditionally, that equipment was fuelled by wood or charcoal; in recent years many homes have converted to kerosene burning.[1] Smoke from wood fires has been suggested as a factor in lung cancer aetiology,[2] and cooking with kerosene stoves has been associated with lung cancer in women in Hong Kong.[3]

If nearly all Japanese women were exposed similarly to home pollution, this phenomenon would not present an epidemiological problem. However, there is some evidence that the more well-to-do tend to have greater separation between living and cooking quarters and to use electric heaters instead of charcoal or kerosene burners.[4] Thus women in better economic circumstances may not be exposed to the same level of pollutants as women in lower-income households.

The additional problem is that smoking habits may be related to socioeconomic status. Smoking has been shown to be related to social class in Western countries such as the United States and United Kingdom.[5-8] While similar data on smoking habits and socioeconomic status do not appear to be available for Japan, some information is available to show an inverse relationship between economic status and smoking. In the table I give averaged monthly household expenditure on tobacco by annual income extracted from the 1980 *Japan Statistical Yearbook*.[9]

Expenditure on tobacco in Japan according to income

Annual income (1000 yen)	Monthly household expenditure on tobacco (yen)
<2900	1424
2910-4900	1260
>4900	1213

It is suggested that less smoking may take place in the more well-to-do households, coupled with less exposure to soot and fumes from cooking and heating appliances. In contrast, there may be more smoking and greater pollution in less wealthy households. Thus, while Dr Hirayama may indeed have observed an important phenomenon, the reasons for the increased rates of lung cancer in the wives of smoking husbands may not lie in their exposure to tobacco smoke. Rather, the greater exposure of women from lower socioeconomic classes to the combustion products of cooking and heating fires may account for the observed increase in lung mortality. Dr Hirayama's finding of increased standardised lung cancer mortality rates in rural areas, where charcoal and kerosene heating have tended to persist, when compared to urban areas, where there is a higher proportion of "modernised" homes with electric heating, would seem to support this hypothesis.

Dr Hirayama is an experienced member of the epidemiology community and it is hoped that he will expand his investigation to include the effects of indoor pollution to which Japanese women may have been exposed.

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2910-4900	1260
>4900	1213

It is suggested that less smoking may take place in the more well-to-do households, coupled with less exposure to soot and fumes from cooking and heating appliances. In contrast, there may be more smoking and greater pollution in less wealthy households. Thus, while Dr Hirayama may indeed have observed an important phenomenon, the reasons for the increased rates of lung cancer in the wives of smoking husbands may not lie in their exposure to tobacco smoke. Rather, the greater exposure of women from lower socioeconomic classes to the combustion products of cooking and heating fires may account for the observed increase in lung mortality. Dr Hirayama's finding of increased standardised lung cancer mortality rates in rural areas, where charcoal and kerosene heating have tended to persist, when compared to urban areas, where there is a higher proportion of "modernised" homes with electric heating, would seem to support this hypothesis.

Dr Hirayama is an experienced member of the epidemiology community and it is hoped that he will expand his investigation to include the effects of indoor pollution to which Japanese women may have been exposed.

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A Large-Scale Census-Based Cohort Study in Japan

T. Hirayama
Institute of Preventive Oncology, Tokyo

41 figures and 37 tables, 1990

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Contributions to Epidemiology and Biostatistics

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The author and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Franz Adlkofer

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Franz Adlkofer

The Problems of Passive Smoking

People are faced day and night with reports about the presence of noxious, in particular carcinogenic, substances in almost all spheres of life. They are found in our food and drink etc. just as much as in the air we breathe. Thereby the impression is created that all these substances are man-made and the result of industrialisation. In truth many of them occur throughout nature and mankind has been exposed to them since the beginning of phytogenesis. In order to survive at all in such a hostile environment, Man has over millions of years developed effective defence systems, already recognised by Paracelsus and reflected in his doctrine: "dosis facit venenum". Whether this applies to carcinogenic substances too, which would be plausible, is at present the subject of controversial discussion. There are those who are convinced that the biological defence systems only break down if they are metabolically over-loaded; there are ample examples of this. They do not believe that the simple mechanistic view is tenable according to which injury to health occurs in direct proportion to the cancerogenic substances absorbed and thus believe in the existence of a threshold in respect of these substances. In contrast, there are others who will not budge from their opinion that even one cigarette per day or one puff from a cigarette or even the fact of passive smoking will contribute to bring about cancer some decades later. This controversy will endure until we understand the molecular and cellular mechanisms which trigger off cancer in individuals -- and we are still far from that day. The following article is intended to show the present state of scientific research into the problem of passive smoking, which leads us to the conclusion that a minimal risk to health through passive smoking cannot be either excluded or proved.

The historical background

In Europe the battle of Authority against smoking goes back to the 17th century. The many prohibitions against smoking issued in almost all countries were based on a variety of reasons, but hardly ever on the grounds of it being a nuisance, let alone a possible risk to the health of non-smokers. It was left to our Federal Government to recognise, at the beginning of the seventies, "with adequate certainty that the proved injury to health through smoking can also occur through passive smoking in the same way although to a lesser degree" (Bundestag Printed Matter 7/2070). This is the more astonishing as, at that time, scientific research into passive smoking had not even begun in earnest. To what extent such an evident analogism can be used

to justify a statement of that nature was not even investigated at the time. At any rate the world of science felt called upon to pay more attention to the problem of passive smoking. In so doing it was following a world-wide trend which had been set in motion and which was being maintained by the ever more heated discussion about the risks to health through smoking. To date a vast number of papers have been published and many congresses held on the subject of passive smoking. Two original papers and two review articles stand out from the almost overwhelming mass of literature. The two original papers, of which one is scientifically without value and the other subject to a great deal of doubt, have contributed to heating up the discussion about passive smoking throughout the world, whereas the review articles, which differ greatly in quality, have done the same within the Federal Republic.

In 1980, the 'New England Journal of Medecine' published the results of a study by White and Froeb showing that chronic exposure to tobacco smoke at work brought about a significant deterioration in the lung function of non-smokers. So far as the authors were concerned, and those who wanted to believe it, this paper for the first time provided proof of the harmfulness of passive smoking. In fact, however, the results obtained by White and Froeb are not scientically tenable. Professor Lebowitz, one of the co-authors of the American Surgeon General's Report, for instance, declared the following at a hearing in Washington: "The basic problem with the White and Froeb study is that it was ill-planned from the epidemiological point of view. The difficulties are inherent in the paper from its very beginning to the statistical analysis and affect all data and the conclusions. The fact that some time between 1976/77 and the time when the study was published 3000 people were taken out of it, whereby the results suddenly became significant, is particularly remarkable. Unfortunately Dr. White cannot remember why he removed these 3000 people from his study." Following a visit to Dr. White, Professor Gostomzyk, Head of the Health Office of the city of Augsburg and Dr. Heller of the Institute for Mathematical Economic Theory of Karlsruhe University commented in a similar manner. They summarised their impressions as follows: "The working methods of Dr. White are not those of a scientist but are more like those of a layman convinced of his ideas". Quite irrespective of this shattering assessment the work fulfilled its purpose in that for the first time it rendered smokers responsible for damaging the health of their fellow-men. It enabled Dr. White who is a sports teacher and active in the Californian anti-smoking movement to influence a plebiscite in California on smoking in public places and at work. In addition it is quoted by other authors whenever the injurious effect of passive smoking on the lung function of non-smokers is emphasised. In "Berichte (Reports) 3/86" of the Federal Office for the Environment it is even regarded as the only paper of its kind which can withstand criticism. It is therefore not to be wondered at that the Council of Experts on the Environment

used it to bolster up the ideas contained in its recently completed Expert Opinion.

One year later there appeared in the 'British Medical Journal' the publication of Hirayama's further results of a cohort-study begun in 1965 on the influence of life-style and environmental factors on the origins of disease in Japan. A side-result of this study had been that non-smoking wives of smoking husbands die more frequently of lung cancer and - for whatever reason - commit suicide more often than non-smoking wives of non-smoking husbands. This study, which even today remains the most important of all the epidemiological studies undertaken into the problems of passive smoking and which has provided a new dimension for the discussion of this issue, constitutes a watershed. For some it is the final proof of the risk of cancer through passive smoking, for others it is no more than an unscientific fabrication in which figures were manipulated until they attained the desired level of significance for the dose/response ratio. Whatever may be right, the study leaves many questions open and there are hypotheses on the basis of which the findings can be explained without reference to passive smoking. The real scandal however is that Dr. Hirayama is neither willing nor can be forced to lay his original data open for examination. Only a few weeks ago he answered with a smile an invitation to do so at a Tokyo symposium.

In 1985 the Senate Commission of Enquiry into Substances Noxious to Health included passive smoking in the MAK-List. In a detailed statement of motive, it endeavoured to justify its suspicion of passive smoking as being carcinogenic. In so doing the Senate Commission was aware of the fact that the causal link betwen passive smoking and lung cancer is the subject of controversial discussion and that the available epidemiological findings can at best indicate a serious hypothesis. According to its principles, carcinogenic substances should if possible be wholly shunned at work or, where this is not possible, they should be kept as low as possible, since the Commission does not assume there to be threshold values for these substances. Because tobacco smoke contains mutagenic and carcinogenic substances the Commission considers the inclusion of passive smoking in the MAK-List to be obligatory and it even feels that this would have been possible many years ago. It does, however, seem doubtful whether any relevant statement concerning dangers to health through passive smoking can be made on this basis without it being backed by any epidemiological findings or animal experiments. From the point of view of preventive medecine it would be necessary to quantify the risks in order to establish priorities for protective measures. But it is just this that the Senate Commission declares to be impossible at present.

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This year the Tübingen toxicologist Professor Remmer, who is a member of the Senate Commission and a zealous supporter of the inclusion of passive smoking in the MAK-List, published a paper in the 'Deutsche Medizinische Wochenschrift' in which tobacco smoke is described as the most dangerous noxious substance to man in the air we breathe. He had noticed that in many epidemiological studies the difference in the risk of lung cancer through smoking and through passive smoking was too small for the risk incurred through passive smoking to be plausible. To explain this evident discrepancy Professor Remmer based himself on some very arbitrarily selected literature in order to draw up a theory according to which active smoking may cause far less cancer than passive smoking. It is believed that certain compounds contained in the mainstream smoke induce enzymes which detoxify the carcinogenic substances. Whereas in the sidestream smoke, to which passive smokers are exposed, these compounds are only found in ineffectively weak concentrations. Therefore, in contrast to what happens in the case of active smoking, very small quantities of inhaled carcinogenics could become fully effective. This theory is not supported by any scientific findings. Interpretation has taken the place of findings, which stands the process of acquiring knowledge on its head, as has been noted by the Research Council on Smoking and Health in a letter to the editor of the 'Deutsche Medizinische Wochenschrift'.

The Driving Forces

Bearing in mind the many risks to health to which we are daily exposed, passive smoking, which is considered a non-problem by many scientists, takes up an astonishing amount of room in public discussion. The question arises as to what may be the reasons which, despite the factual situation, keep the discussion on passive smoking going, and render it ever more passionate. I should like to pinpoint some of these reasons as follows:

Environmental consciousness has considerably increased in the course of the past decade. Therefore successful efforts have been made to reduce air pollution in our large cities and industrial conurbations as well as at the place of work without, however, even nearly attaining the desired goal of nil-pollution. More attention is being paid to indoor air pollution to which tobacco smoke contributes to a considerable degree because of the wide-spread habit of smoking. Modern methods of chemical analysis make it possible to discover even the minutest quantities of noxious substances. Although this is far from telling us anything about their toxicological significance, a need to act is created because people believe that ever less pollution must lead to ever better health. They leave out of account the doctrine of Paracelsus, which says that "the dose makes the poison."

Responsible politicians interested in health issues are bound to act in the interests of the people entrusted to their care, as soon as they are "adequately certain" that passive smoking may lead to a health risk for non-smokers. They cannot afford to wait until "a line of sick people, invalids and dead bodies can be produced to prove that they have fallen victim to passive smoking" as it was expressed in a Bundestag Printed Matter of 1974. Since politicians can hardly themselves have the scientific training to assess the risks, they must rely on the knowledge of others. This offers lobbies a chance to influence health policy decisions in one way or another.

A pluralistic society such as ours has lobbies. And it is they who have by now removed the subject of passive smoking from scientific discussion and have put it on the political stage. It would be wrong to impute this to bad intentions. Inadequate or biassed occupation with the problem, or general insecurity with regard to scientific comprehension, are quite enough.

- There are certain branches of industry and their corresponding trade associations who seem to believe that the term occupational cancer has lost its raison d'être. So far as they are concerned lung cancer stems from smoking only, and in the case of a non-smoker, well then it is due to passive smoking. The trade unions would be well advised to discover the error of their ways in good time and to protect their members from its pernicious consequences.

- There are anti-smoking movements which, after years of guerilla warfare against smoking, have had to realise that smokers react with surprising indifference to reproaches of self-inflicted injury or being a nuisance to others. It is the aim of the anti-smoking movements to bring about a smoke-free society by the year 2000. The means to attain this end is the social ostracism of smoking. No argument is better for this purpose than to maintain that by their inconsiderate behaviour smokers endanger the health of their fellow-men.

- Certainly the cigarette industry would also have liked to intervene in the process of shaping public opinion. After all, 90% of the public by now believe that the harmfulness of passive smoking has been proved and is hardly less than that of active smoking. But the industry's chances are poor, since it has an economic interest in the matter, and has a reputation for greed into the bargain.

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Tobacco Smoke in Enclosed Spaces

Tobacco smoke in enclosed spaces consists of a mixture of about 15/20% exhaled mainstream smoke and 80/85% sidestream smoke. The mainstream component is very different from the sidestream component. Both originate in the burning zone of the cigarette, but at different temperatures. Mainstream smoke is inhaled by the smoker and in part exhaled again. Sidestream smoke originates between the puffs taken by the smoker and is released directly into the room, where it is diluted. Mainstream and sidestream tobacco smoke in a room are composed of a gaseous and a particle phase. More than 90% of the weight is accounted for by the gaseous phase. Quantitatively significant compounds are: vapour, carbon dioxide, carbon monoxide, ammonia, aldehyde and nicotine. Tobacco smoke in the room contains mainly the same substances as the mainstream smoke. Table 1 shows the concentrations of main and sidestream smoke in the air of the enclosed space under approximately realistic conditions.

There does not at present exist any reliable marker for tobacco pollution in enclosed spaces. The reason for this is that the sidestream smoke from cigarettes, cigars and pipes differs from product to product, that smokers as individuals and as between individuals produce different amounts of main and sidestream smoke, and that tobacco smoke in the air rapidly changes its composition as it ages. In addition, air in an enclosed space often contains substances which do not stem from tobacco smoke, and in some cases this kind of pollution can be greater than that caused by the tobacco smoke. Nicotine seems to be the most suitable marker for tobacco smoke in an enclosed space; 95% of it is part of the gaseous phase and not of the particle phase as in the mainstream smoke. Nicotine occurs in the enclosed air only if in fact there has been smoking. Carbon monoxide and other substances are less suitable as markers. They can only be employed where the basic pollution has been established first.

Undiluted sidestream smoke contains larger quantities of some carcinogenic substances such as polycyclic aromatic carbohydrates and volatile N-nitroso-compounds than are contained in the mainsmoke stream. Accordingly, the carcinogenic potential of sidestream smoke could be a little greater than that of the mainstream smoke, given equal quantities of substance. In their 1967 test on the skin of mice Wynder and Hoffman found that an application of condensate from sidestream smoke caused more tumors than an application of condensate from mainstream smoke. The gaseous phase was wholly neglected in this experiment. The same working party carried out inhalation experiments with hamsters, but no histological results are yet available. Astonishingly enough, however, the animals treated with main- and sidestream smoke lived longer than the untreated control animals.

One problem in comparing the carcinogenic potential of main- and sidestream smoke lies in the fact that mainstream smoke is immediately inhaled whilst sidestream smoke ages when released into the air and thereby loses much of its toxic potential. It is not known to what extent this is also true for its mutagenic and carcinogenic potential. The one thing that is sure is that in the course of time its composition changes considerably because of dilution, evaporation, oxidation, other chemical reactions, and selective surface absorption. The few available comparative studies of main- and sidestream smoke, which were mainly carried out to measure mutagenic potential are either faulty or have produced contradictory results. Nevertheless, some scientists still insist that tobacco smoke in an enclosed space is more carcinogenic than mainstream smoke. This hypothesis is based on a comparison of fewer than 100 substances -- of the 3800 compounds identified in tobacco smoke, this is a very modest fraction. It leaves out of account both the very considerable dilution of sidestream smoke in the enclosed air and the ageing process.

As compared with former times, sidestream smoke to-day releases fewer mutagenic and carcinogenic substances since the smokers of modern cigarettes produce more mainstream and less sidestream smoke because of the halving of the nicotine and condensate content which has taken place over the years. The reason for this lies in the lower tobacco content in cigarettes and improved filter techniques. It is likely that the reductions reach up to 20%. The figures obtained with smoking-machines, which argue in favour of a disproportionately high release of carcinogenic compounds in the sidestream smoke do not reflect this development because smoking-machines simulate the smoking habits of the nineteen-fifties.

Studies undertaken so far show that the components of tobacco smoke are variously distributed in the main- and sidestream as well as in the indoor air. For that reason alone it is not possible to extrapolate from the risks of the smoker to those of the passive smoker.

Inhalation of Tobacco Smoke through Passive Smoking

Effects of passive smoking on health can be expected if the noxious substances thus inhaled are sufficient to overcome the physiological defence system of man. Only a little more than 10% of the particle phase of tobacco smoke is retained in the respiratory passages according to Hiller. Only part of this is resorbed, since the lungs have an effective cleansing mechanism. In contrast to this, something between 45% and 95% of the particle phase of the mainstream smoke is retained in the lungs of the smoker, this smoke being highly concentrated as compared with the tobacco smoke in the enclosed space. Of

the gaseous phase of tobacco smoke in the enclosed air, mainly those compounds are resorbed in the nose and throat area and the upper respiratory tracts, which are easily soluble in water and/or chemically highly reactive. They are substances such as: formaldehyde, acetaldehyde acrolein, acetone, ammonia, and possibly also nicotine, ozone and free radicals. Insoluble and not highly reactive compounds such as carbohydrate can indeed reach the alveolar space of the lungs, but their rate of retention is very low. The mainstream smoke contains the major part of carcinogenic compounds in the particle phase. Whether this is also true of tobacco smoke in an enclosed space is not known, though there are some indications that this may be so.

Table 1

Important substances of tobacco smoke in mainstream smoke (HSR) and sidestream smoke (NSR) of cigarettes in an enclosed air space under approximately realistic conditions.

Substance	HSR Quantity/ Cigarette	NSR	Concentration in enclosed space
Carbon monoxide (CO)	2-20 mg	46-61 mg	3,6-24 mg/m3 (3-20) ppm.
Nitrogen oxide (NO)	0,07-0,17 mg	1,6-3 mg	83-333 ug/m^3 (50-200 ppb)
Nitrogen dioxide (NO_2)	n.n.	0,16 mg	19-132 ug/m^3 (10-70 ppb)
Ammonia (NH_3)	50 ug	5300-8500 ug	100-450 ug/m^3
Cyanide (HC)	150-550 ug	100-250 ug	10-120 ug/m^3
Formaldehyde	20-90 ug	450-1500 ug	20-100 ug/m^3
Acetaldehyde	18-1400 ug	2400 ug	400-500 ug/m^3
Acrolein	25-140 ug	925 ug	15-25 ug/m^3
Nicotine	0,5-2 mg	3-4 mg.	20-100 ug/m^3
Phenol	10-130 ug	270-320 ug	< 1-20 ug/m^3
Benzol	10-100 ug	488 ug	5-16 ug/m^3
Volatile Nitrosamines			
NDMA	0,2-20 ng	155-398 ng	5-70 ng/m^3
NDYR	2,4-29 ng	7-150 ng	1-5 ng/m^3
Nitrosamines specific to tobacco			
NNN	0,20-5,5 ug	0,15-6 ug	< 1-6 ng/m^3)
NNK	0,1-4,2 ug	0,2-0,8 ug	< 2-11 ng/m^3)
Benzo(a)pyrene	10-50 ng	25-103 ng	3-25 ng/m^3
Cadmium	100 ng	430-720 ng	9-31 ng/m^3
Particles (TPM)	5-30 mg	20-50 mg	0,1-0,5 mg/m^3

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Attempts have been made to quantify, with the aid of various biochemical markers, the absorption of tobacco smoke through smoking and passive smoking. A reliable marker should be tobacco-smoke-specific and should, in resorption, behave as those substances which entail the greatest risk to health. Compounds which are resorbed in the nose and throat area should therefore, not be used to assess the risks of lung cancer. Biochemical markers which would answer these requirements are not yet known. The most suitable seems to be cotinine, a nicotine metabolite. Nicotine and cotinine in body fluids prove exposure to tobacco. However, it is difficult, or even impossible, to quantify the exposure. In passive smoking nicotine acts only partly like the mutagenic and carcinogenic compounds of the particle phase. Tobacco smoke in enclosed air contains it in the gaseous phase, as has been pointed out, and not in the particle phase as is the case with mainstream smoke. Nicotine occurs as a base and is more quickly resorbed in this form than the protonised nicotine of the mainstream smoke. To some extent this already happens in the nose and throat area and the upper respiratory tracts. Nicotine, the half-life of which is short at 30 minutes is also differently metabolised as between one individual and another. In passive smokers the half-life of cotinine, which is 15 to 25 hours in smokers, is further reduced. The cotinine level in the serum, and the nicotine and cotinine excretion in urine are considerably influenced thereby, so that they are only of limited value as a measure for the absorption of tobacco smoke. In no circumstances should such data be considered suitable for the assessment of the lung-cancer risk. This is true even where they may show a correlation with tobacco pollution, as has emerged from some experiments. Nonetheless some authors maintain the view that passive smokers inhale up to 1% of the amount of tobacco smoke inhaled by smokers and conclude therefrom that they are exposed to about 1% of the risk to which smokers are exposed. Table 2 shows the nicotine and cotinine concentrations in the body fluids of smokers and passive smokers.

Alongside nicotine, carboxyhaemoglobin and thiocyanate contained in serum are also used to measure the exposure of non-smokers to tobacco. They are however even less suited than nicotine or cotinine to establish the exposure to tobacco. Carbon monoxide which is formed in the body's own metabolism normally leads to an approximately 0.7% concentration of carboxyhaemoglobin. As a rule no increase, or only a small increase, is found in passive smokers. It is only under extreme conditions and after an exposure to tobacco of several hours that a carboxyhaemoglobin value of 2% can be attained. Thiocyanate stems from hydrogen cyanide which also occurs in tobacco smoke. Both carbon monoxide and hydrogen cyanide (or cyanide ions) are tobacco-smoke unspecific and can be found in the air or in food, and also in concentrations which can be much higher than those found in tobacco smoke in enclosed spaces.

Groups studied/Exposure	N	Result			Literature
Clinical Staff					
- not exposed (a.m.)	30	Nicotine in urine:	7.5 ±	8.3 ng/ml	Feyerabend et al 1982
- exposed (a.m.)	26	Nicotine in urine:	21.6 ±	28.8 ng/ml	
- cigarette smokers (average inhalers)	32	Nicotine in urine:	1343.4 ±	1699.8 ng/ml	
Patients and Clinical Staff					
- not exposed	22	Cotinine in urine:	2.0 ng/ml (Median)		
- exposed	199	Cotinine in urine:	6.0 ng/ml (Median)		
- Cigarette smokers	131	Cotinine in urine	1645.0 ng/ml (Median)		Wald et al. 1984
Husbands					
- non-smoking wife	101	Cotinine in urine:	8.5 ±	1.3 ng/ml	Wald and Ritchie 1984
- smoking wife	20	Cotinine in urine:	25.2 ±	14.8 ng/ml	
Clerical Staff					
Blood samples at 11.30 and 19.45 (in between, two hours in a smoke-filled bar)			11.30	19.45	
	7	Nicotine in Plasma	0.8	2.5 ng/ml	
		Nicotine in urine	10.5	92.6 ng/ml	
		Cotinine in Plasma	1.1	7.3 ng/ml	Jarvis et al. 1983
		Cotinine in Saliva	1.5	8.0 ng/ml	
		Cotinine in urine	4.8	12.9 ng/ml	
Ambulant patients					
- non-smokers, not exposed	46	Nicotine in plasma:	1.04 ng/ml		
		Nicotine in urine:	3.87 ng/ml		
		Cotinine in plasma:	0.82 ng/ml		
		Cotinine in saliva:	0.73 ng/ml		
		Cotinine in urine:	1.55 ng/ml		Jarvis et al. 1984
- non-smokers, exposed	54	Nicotine in plasma:	0.77 ng/ml		Russel 1987
		Nicotine in urine:	12.11 ng/ml		
		Cotinine in Plasma:	2.04 ng/ml		
		Cotinine in saliva:	2.48 ng/ml		
		Cotinine in urine:	7.71 ng/ml		
- Smokers	94	Nicotine in plasma:	14.6 ng/ml		
		Nicotine in urine:	1749.9 ng/ml		
		Cotinine in plasma:	275.2 ng/ml		
		Cotinine in saliva:	309.9 ng/ml		
		Cotinine in urine:	1391.0 ng/ml		
Staff					
- Clerical staff not exposed	20	Cotinine in plasma:	5.2 ±	1.5 ng/ml	
		Cotinine inurine:	8.3 ±	6.7 ng/ml	
- Waiters, Waitresses exposed	26	Cotinine in plasma:	10.0 ±	4.0 ng/ml	Husgafvel - Pusiainen et al. 1987
		Cotinine in urine:	56 ±	37 ng/ml	
- Smokers	22	Cotinine in plasma:	246 ±	91 ng/ml	
		Cotinine in urine:	1578 ±	765 ng/ml	

Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

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Groups studied/Exposure	N	Result	Literature
Clinical Staff			
- not exposed (a.m.)	30	Nicotine in urine: 7.5 $\pm$ 8.3 ng/ml	Feyerabend et al 1982
- exposed (a.m.)	26	Nicotine in urine: 21.6 $\pm$ 28.8 ng/ml	
- cigarette smokers (average inhalers)	32	Nicotine in urine: 1343.4 $\pm$ 1699.8 ng/ml	
Patients and Clinical Staff			
- not exposed	22	Cotinine in urine: 2.0 ng/ml (Median)	
- exposed	199	Cotinine in urine: 6.0 ng/ml (Median)	
- Cigarette smokers	131	Cotinine in urine 1645.0 ng/ml (Median)	Wald et al. 1984
Husbands			
- non-smoking wife	101	Cotinine in urine: 8.5 $\pm$ 1.3 ng/ml	Wald and Ritchie 1984
- smoking wife	20	Cotinine in urine: 25.2 $\pm$ 14.8 ng/ml	
Clerical Staff			
Blood samples at 11.30 and 19.45 (in between, two hours in a smoke-filled bar)	7	11.30 / 19.45	
		Nicotine in Plasma 0.8 / 2.5 ng/ml	
		Nicotine in urine 10.5 / 92.6 ng/ml	
		Cotinine in Plasma 1.1 / 7.3 ng/ml	Jarvis et al. 1983
		Cotinine in Saliva 1.5 / 8.0 ng/ml	
		Cotinine in urine 4.8 / 12.9 ng/ml	
Ambulant patients			
- non-smokers, not exposed	46	Nicotine in plasma: 1.04 ng/ml	
		Nicotine in urine: 3.87 ng/ml	
		Cotinine in plasma: 0.82 ng/ml	
		Cotinine in saliva: 0.73 ng/ml	Jarvis et al. 1984
		Cotinine in urine: 1.55 ng/ml	
- non-smokers, exposed	54	Nicotine in plasma: 0.77 ng/ml	Russel 1987
		Nicotine in urine: 12.11 ng/ml	
		Cotinine in Plasma: 2.04 ng/ml	
		Cotinine in saliva: 2.48 ng/ml	
		Cotinine in urine: 7.71 ng/ml	
- Smokers	94	Nicotine in plasma: 14.8 ng/ml	
		Nicotine in urine: 1749.9 ng/ml	
		Cotinine in plasma: 275.2 ng/ml	
		Cotinine in saliva: 309.9 ng/ml	
		Cotinine in urine: 1391.0 ng/ml	

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staff			
- Clerical staff not exposed	20	Cotinine in plasma: 5.2 ± 1.5 ng/ml Cotinine inurine : 8.3 ± 6.7 ng/ml	
- Waiters, Waitresses exposed	26	Cotinine in plasma: 10.0 ± 4.0 ng/ml Cotinine in urine: 56 ± 37 ng/ml	Husgafvel - Pusiainen et al. 1987
- Smokers	22	Cotinine in plasma: 246 ± 91 ng/ml Cotinine in urine: 1578 ± 765 ng/ml	

Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

According to a study carried out by the Bremen Institute for Preventive Research and Social Medecine we must assume that the total exposure of non-smokers lies in the private sphere to more than 60%, the main cause being smoking spouses. However, in working men and women exposure at the place of work also plays an important part. According to a study by Letzel and Johnson the daily exposure to tobacco smoke amounts to between 1 to 2 hours for men and a little less for women. The duration of exposure fluctuates according to age and sex.

Epidemiological Findings - Lung Function in Adults

To date eight epidemiological studies are available, of which four point to a deterioration of lung function as a result of passive smoking. One of them is the paper by White and Froeb referred to earlier on, which does not attain scientific standards but is nevertheless the one most frequently quoted as evidence of lung damage through passive smoking. In the four other studies, including one from the Federal Republic, no influence of passive smoking on lung function was found. The problem with studies of this kind is that there are numerous environmental factors which can impair lung function and that it is difficult or even impossible to isolate one single cause. This is the view also taken in the 1986 Report of the Federal Environment Office.

Lung Function in Children

There exist at least twenty epidemiological studies, all carried out in a similar manner, in which the influence of parental smoking on the lung function of children is examined. Thirteen of them conclude that smoking by parents, especially by mothers, impairs the children's lung function. The differences between such children and others whose parents did not smoke were small and varied between less than 1% and 8%. In an analysis presented on the occasion of the "Indoor Air Conference '87" in Berlin, Professor Witorsch of the Virginia Commonwealth University (USA) doubted even this order of magnitude. He pointed out that in all these studies the socio-economic status of the parents and their children had been either left out of account altogether, or had been only very superficially taken into consideration. The socio-economic status however is related to smoking as well as to other factors which influence the measurement of children's lung function. Some of these are different attitudes to learning and an absence of motivation, which can have a negative effect on the test result. Moreover it is known that, as compared with non-smokers, smokers inhabit on the whole a lower socio-economic status which implies less favourable housing so far as area, size and equipment of accommodation are concerned, and with a less health-conscious life-style of the family with regard to nutrition, sports and other habits and

attitudes. Here again it is virtually impossible in a statistical analysis to exclude all these 'confounding factors' as potentially contributory causes for a deterioration in the lung function and the appearance of pulmonary symptoms. In fairness it ought therefore to be conceded that the question as to the extent to which passive smoking plays a part in all this has not yet been satisfactorily answered. The suspicion however remains.

Coronary Heart Diseases

So far a total of 7 epidemiological studies are known which deal with the possible influence of passive smoking in the genesis of coronary heart diseases. In his above-mentioned study Hirayama found that in non-smoking wives of smokers of more than 20 cigarettes per day, there was a relative risk of 1.35. He did not, however, standardise other coronary risk factors such as hypertension or hyper-cholesterol-aemia. His observation is the more astonishing as in Japan smoking as such is of only limited significance for coronary heart disease. Garland and collaborators carried out a case-control study on wives of smokers and ex-smokers and established a relative risk of 2.7, which is marginally significant. Not to mention a few methodological problems which arise from this study, it is most remarkable that 15 of the 19 deaths were of wives of ex-smokers. This contradicts the findings relating to smokers, whose relative risk after giving up smoking declines rapidly and after a few years becomes the same as that of non-smokers. Three of the remaining studies tend towards establishing a link between passive smoking and coronary heart disease; two, including that by Garfinkel which is comparable to that by Hirayama, do not do so. The value of this study is doubted even in the mainly politically-motivated report of the American Surgeon General. Too many problems of method seem unanswered and the doubts concerning the plausibility of the results obtained so far are evident. The risk of death through a myocardial infarct is two to three times higher in our Western societies for smokers than for non-smokers.

It seems that smoking combines with other existing risk factors rather than being an independent risk factor itself. Nicotine and carbon monoxide which in theory are supposed to be responsible for the increased coronary risk to smokers cannot be potential causes as passive smokers absorb them only to a very small extent. This being so, Professor Schmähle was right when on one occasion he asked what could be the 'devilish substance' in tobacco smoke which could bring about such an increased coronary risk in indoor air.

Lung Cancer

In at least eight cohort-studies and 50 case-control studies a significant correlation was established between smoking and lung cancer. The relative risk of lung cancer to male smokers

of one to ten cigarettes per day covers a span from 1.9 to 4.6. Where more than 25 cigarettes are smoked it rises to between 4.6 and 25.1. Since indoor tobacco smoke also contains mutagenic and carcinogenic substances -- though in much smaller quantities than in the mainstream smoke inhaled by the smoker -- the question whether passive smoking may bring about an increase in the risk of lung cancer is perfectly legitimate. As in the case of smoking, epidemiological studies are the proper means to discover any link that may exist. But because the risk to be expected is much smaller, these studies must be planned and carried out as faultlessly as possible. Otherwise we are likely to get artefacts rather than results.

So far three cohort studies are available, of which one does not permit any conclusion to be drawn because of the small number of cases: only six non-smoking men and eight non-smoking women. The American paper by Garfinkel does not present any link between passive smoking and lung cancer. In contrast, Hirayama believes, in the paper already referred to, that he can prove the existence of a significant dose-response ratio. Because mass studies are much superior to case control studies so far as the force of their evidence is concerned, and because Hirayama's findings have so far provided the strongest arguments in favour of a cancer risk through passive smoking, I should like to take a closer look at his work. At a symposium a few weeks ago in Tokyo, Professor Überla, a former chairman of the Federal Health Office pointed out the following shortcomings of the paper in the presence of Dr. Hirayama:

- The paper was not planned in order to test the hypothesis that passive smoking is, or is not, associated with lung cancer;
- The group examined was not representative of Japan so that there may have been a bias in selection;
- The indicator for exposure to passive smoking -- being married to a smoking husband -- is neither reliable nor valid and it is not specific;
- The indicator for the potential consequences of passive smoking -- lung cancer as the cause of death in the death certificate -- is neither reliable nor valid;
- Various 'confounding factors' such as exposure at place of work, general air pollution, differences in nutrition, the type of medical treatment, etc., were not taken into account;
- A possible bias in the classification of women as non-smokers was not excluded, so that it may be assumed that there were some smokers amongst the non-smokers;

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- Almost nothing is known about the 200 deaths reported. There is not a single medical history available and histological findings and reports on autopsies are available in only 11.5% of the cases.

In their re-analysis of Hirayama's data, Uberla and Ahlborn found that the conclusions drawn by Hirayama on the basis of the data published so far are not cogent. When adjusted to the normal age-distribution in Japan the risk of lung cancer due to passive smoking disappeared altogether. In his address in Tokyo, Professor Kilpatrick of the Virginia Commonwealth University (USA) unreservedly agreed with this assessment.

Apart from the cohort studies we now have 19 case control studies. The great majority of these find a relative risk of > 1.0 for lung cancer through passive smoking. The risk-increase which reaches a maximum of 3.23 is significant in only a small number of studies, and a dose/response ratio is established only rarely. Case control studies in which relative risks of 2 or less, i.e. low risk associations, are to be discovered must be faultlessly planned and carried out if they are to allow any conclusion to be drawn at all. Otherwise an increased risk found could be due to a bias or confounding factor. It does not really matter whether such a risk increase is significant or not. After all, significance is no more than a yardstick for the probability of the fortuitously obtained figure being really different from the one expected, it being assumed a priori that the classification of cases is not governed by additional factors.

The first Report by the American Surgeon General, the 1964 Terry-Report, describes the criteria to be met by epidemiological studies in order that a causal link may be assumed. In his review paper "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?" just recently published in the 'International Archives of Occupational and Environmental Health', Professor Uberla notes that in the epidemiological studies published so far these criteria have not, or only partly, been met. A similar conclusion was arrived at by Professor Wynder of the New York American Health Foundation in his address in Tokyo a few weeks ago. The following must be taken into consideration when a causal link is examined:

- At a relative risk of <3 or even <2 the strength of the association is small in all studies. Therefore it would have been particularly important carefully to avoid possible mistakes of method, which was certainly not done. On the other hand there can be no doubt that even a slightly increased risk, if real, would be of great importance from the point of view of public health, given the widespread phenomenon of passive smoking.

- As to the concordance of results within a study or between studies, many questions remain unanswered. Thus not all studies establish a link between passive smoking and lung cancer. In some cases such a link can be shown only through an analysis of sub-groups. In some studies the adenocarcinoma-rate only seems to have increased whereas in others it is only the rate of epithelium-carcinoma.

- Nor is the specificity of association, apparent in the relationship between the exposure and its consequences, properly assured. Neither the measure of exposure -- usually obtained by asking about the spouse's smoking habits -- nor the diagnosis of lung cancer are valid or specific in the light of available experience. In the light of Garfinkel's case-control study Wynder showed how difficult it is to carry out questioning correctly. If the questions were answered by the patient himself, the relative risk came to 1.0, if the spouse answered, it was 0.92, and if the replies came from either daughter or son the figure was 3.19, and when acquaintances were asked, it dropped to 0.77. Despite all these contradictions Garfinkel's study is regarded by some as a further proof of the risk of lung cancer through passive smoking because of its overall significantly-increased relative risk of 2.1. In fact however, in view of the problems highlighted, it would rather seem to prove the opposite. According to Lee the possibility of misclassification constitutes the greatest problem for epidemiological studies of passive smoking, and especially for case control studies. Misclassification quite simply has its origin in wishful thinking to which patients, relatives and researchers may be prone. Because of the human need to find a cause for a blow of fate the former tend to overestimate passive smoking as a possible cause, and the latter would like to see a preconceived opinion confirmed. Garfinkel and collaborators in fact point to the possibility of misclassification after they were compelled to find that about 40% of all patients registered as non-smokers in their sick-reports were in fact smokers. Lee calculated that a small percentage of women smokers erroneously classified as non-smokers was sufficient to falsify results and to show an increased risk of lung cancer through passive smoking.

- Problems arise with regard to time relationships. Though all epidemiological studies show that differing periods of latency precede the genesis of lung cancer due to exposure to passive smoking. But there is hardly one study in which passive smoking during childhood or youth has been properly taken into account. Since according to Doll and Peto the period of exposure in terms of life-years seems to be more important than the magnitude of the dose, passive smoking extending from childhood through adolescence into adult age is supposed to be particularly

disadvantageous. Only Correa and collaborators made an effort to cover childhood smoking. They found that the relative risk of lung cancer was 1.0 where the father smoked and 1.66 where the mother did. This increased risk was significant only for male patients and did not apply to female patients. A further argument against the importance of passive smoking as a cause of lung cancer is proferred by Wynder: the risk of lung cancer in non-smokers should in fact have risen over the past decades in parallel with the greater frequency of lung cancer in smokers if passive smoking were a causal factor. This is however not the case.

- In some studies a significant dose/response ratio was found, such as in the cohort study by Hirayama and in the Greek case control study by Trichopoulos. But Überla describes this latter as a text-book example for all those mistakes which should be avoided at all cost in a case control study. There are several studies in which there is no pointer to a dose/response ratio.

- The case for biological plausibility is similar to that of the epidemiological findings. In both cases there is more than enough reason for doubt. First, one may well wonder whether a fraction of the substances inhaled by smokers can really trigger off a relatively high risk of lung cancer through passive smoking. Epithelium carcinoma (Plattenepithelkarzinom) which according to some studies is supposed to be more than normally frequent in passive smokers begins in cilia-bearing cells which must have undergone metaplastic change. Auerbach and collaborators have shown that the preliminary stages of malignant changes in the bronchial tracts of passive smokers, namely metaplasia and dysplasia can hardly be proved and that the cilia of the cells seem to remain intact. It is likely that no preliminary stages of bronchial carcinoma can be detected because passive smoking does not overload the physiological defence system of the lungs. There is much that argues in favour of this view. It is, however, not proved.

Since 1986 one particular form of evaluating epidemiological studies on passive smoking has gained great importance: it is known as meta-analysis and amounts to the merging of all - or at least most - presently available studies for the purpose of increasing the number of cases and thereby to arrive at a more reliable conclusion. The first analysis of this nature led Professor Wald of St. Bartholomew's Hospital, London, to conclude that the relative risk of lung cancer for passive smoking is 1.30 and thus significantly increased. Wald's paper was regarded as proof of the risk of lung cancer to passive smokers by both the American Surgeon General and the National Academy of Sciences. Despite the esteem in which the authorities hold that paper there are

considerable doubts as to whether it is justifiable to merge the results of epidemiological studies of different quality and to evaluate them jointly. At the end of the day the conclusive value of a meta-analysis very clearly declines with the number and magnitude of the errors contained in the studies upon which it is based. Bearing this in mind, **Letzel and Überla carried out a further meta-analysis based only on those epidemiological studies which meet minimal standards of scientific quality.** On the basis of twelve relevant studies they reached the conclusion that if the Trichopoulos-study is taken into account the relative risk amounts to 1.12, and if it is not, the figure declines to 1.08. **That risk-increase however is not significant and remains within the limits of 'statistical smoking'.**

Toxicology of Passive Smoking

In view of the evident difficulties epidemiologists encounter in helping to find out whether there is a link between passive smoking and lung cancer, it is not to be wondered at that the toxicologists have been giving more and more attention to the subject. The findings established so far were discussed in 1986 at a symposium in Essen and in 1987 at congresses in Berlin and Tokyo. The results, most of which were obtained in more or less controlled chamber-experiments are in part contradictory. Persons exposed to tobacco smoke most frequently complain about irritation of the mucus membranes, for which mainly substances contained in the gaseous phase, but probably also in the particle phase, are responsible. Subjective sensations of feeling ill and bad smell are quoted as additional nuisances. According to Professor Winneke of the Institute for Air Hygiene and Silicosis Research of Düsseldorf University early difficulties of this nature occur when the concentration of tobacco smoke corresponds to 5 ppm CO and not, as alleged in an earlier study by Weber and collaborators, at 2 ppm CO. Whereas irritations increase with the duration exposure, the other effects are complained of only during the initial ten to fifteen minutes.

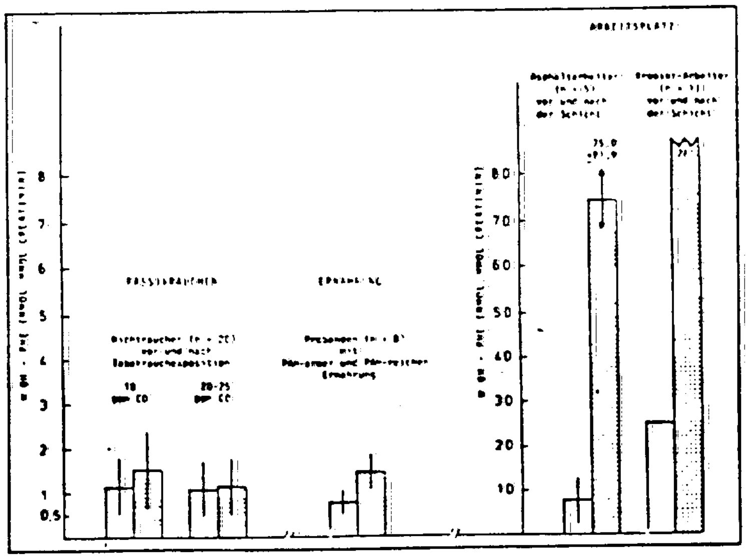
Nicotine, cotinine and thiocyanate in body fluids as well as carboxyhaemoglobin merely show that there has been exposure to tobacco smoke. In order to cover the long-term effects of exposure to tobacco smoke it would seem necessary to examine the absorption and the effect of compounds with genotoxic qualities. Below, the results are presented of a number of experiments which deal with this problem.

Phenanthrene is part of the group of polycyclic carbohydrates (PAH) and is contained in cigarette smoke, diesel exhaust fumes and also in roast pork. Hydroxyphenanthrenes are products of the metabolism of phenanthrene and are rightly considered to be

markers for the absorption of PAH. We were able to show that the excretion of hydroxyphenanthrene in urine does not increase after an 8-hour exposure to tobacco smoke, irrespective of whether the concentration at 10 ppm CO is medium or very high at 20 to 25 ppm CO. (Graph 1). The excretion of hydroxyphenanthrene changes significantly if, after a diet low in PAH, one is provided which is high in PAH. Extremely high excretion of hydroxyphenanthrene is found in workers exposed to high PAH concentrations at work. Data established in co-operation with Professor Grimmer from the Biochemical Institute for Environmental cancer in Hamburg show how widely the PAH impact fluctuates and how secondary the role which passive smoking plays therein.

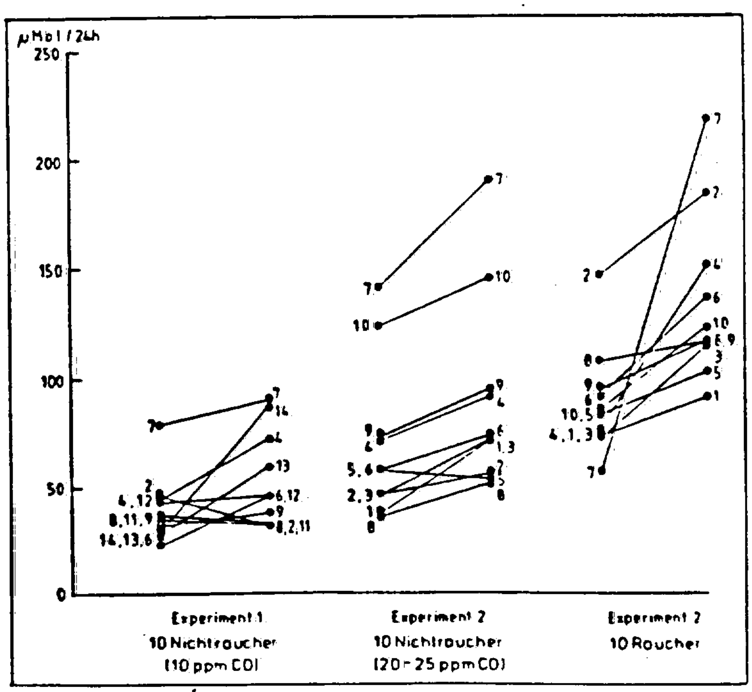
Mercapturic acids (thioethers) are the detoxification products of many electrophile, and thus potentially mutagenic and carcinogenic, substances. Their genesis is catalysed by the glutathion-S-transferase-system and their rate of excretion in urine can be used to measure the impact of these compounds. The excretion of mercapturic acids rises slightly when a non-smoker has been exposed for 8 hours to a tobacco smoke concentration of 10 ppm CO and increases further when this is doubled (Graph 2). As compared with non-smokers, the thioether-excretion is still higher than normal in smokers after an abstinence of 36 hours and, after ten to 20 cigarettes have been smoked, it increases more vigorously than in passive smokers. The higher excretion of thioethers after passive smoking was, by the way, described for the first time and was probably discovered only because the diet of the test persons had been strictly controlled over a period of several days. The results of the experiment carried out in co-operation with Professor Sorsa of the Institute of Occupational Health in Helsinki confirm the view that through passive smoking electrophile substances are absorbed and detoxified. How effective this detoxification is, requires further study.

Mutagenic and carcinogenic substances are excreted in urine if they neither react with macromolecules in the organism, such as DNA, nor are detoxified in metabolism through the various protective enzyme systems. They can be detected in urine through the Ames-Test. In our experiment we found no significant increase in mutagenic activity in passive smokers either after a medium (10 ppm CO) or a high eight-hour exposure to tobacco smoke (20 to 25 ppm CO) (Graph 3). With one exception our results agree with those of other authors so far as the extent of mutagenic activity is concerned. Professor Norpoth's working party of the Institute of Hygiene and Social Medecine of Essen University found an increase in passive smokers which corresponded to that of smokers of four to five cigarettes. The reason for this different result is not at present known and needs to be discovered. Our results suggest that in contrast to smoking, passive smoking leads to the absorption of too few mutagenic or carcinogenic substances for



Graph 1

Hydroxyphenanthrene excretion in urine following PAH absorption during medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, during nutrition both poor and rich in PAH and at selected workplaces.



Graph 2

Thioether excretion in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.

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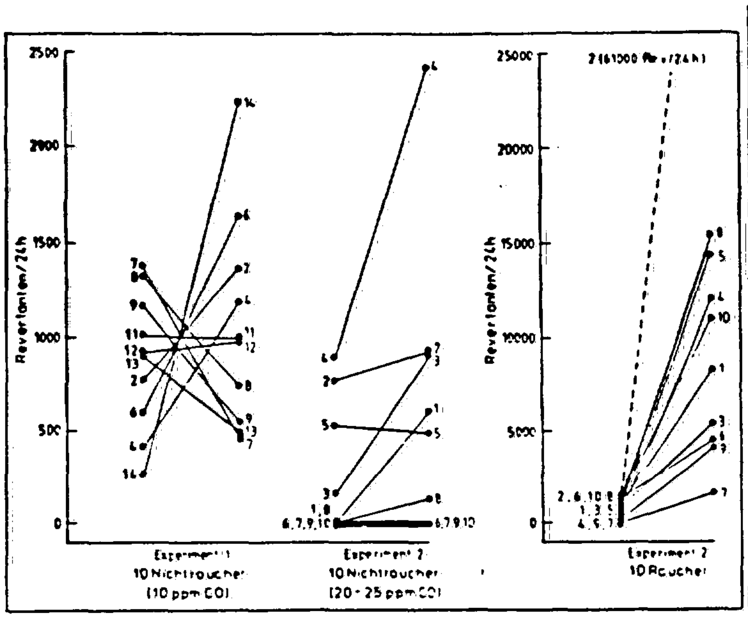

Graph 3

Mutagenic activity in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.

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them to be detected with the Ames-Test in urine. It is however just as possible that these substances can be effectively detoxified in passive smokers through the cellular glutathion-S-transferase-system and other enzymes, which does not seem to be possible in the case of smokers because of the overload with which their metabolism is charged.

Under the impression of the results of the symposium on "Experimental Toxicology on Passive Smoking" in Essen Professor Gostomczyk made the following comment: "Taking into account the results of the Essen symposium we may say that toxicologists have so far no more than epidemiologists rendered more probable the existence of a link between passive smoking and injuries to health." Our findings should be interpreted on the same lines.

Conclusions

Tobacco smoke indoors contains toxic, mutagenic and carcinogenic substances which are inhaled by non-smokers. The concentrations are all low. There does not, at present, exist a marker for indoor tobacco smoke. The reason for this is that the composition of tobacco smoke differs according to the product from which stems, and that it is subject to constant quantitative and qualitative change through ageing. It is almost always mixed with substances of another origin, the concentration of which is frequently higher than that due to tobacco smoke. However, nicotine, which is specific to tobacco smoke, can be used to provide qualitative proof of indoor air pollution through tobacco smoke.

The particle phase of tobacco smoke is retained in the lungs at a rate of a little more than only 10% after inhalation. It may be assumed that a considerable part of it is not absorbed by the organism but is removed from the respiratory passages through the cleansing mechanism of the lungs. Reactive compounds of the gaseous phase and/or such which are easily soluble in water are largely resorbed in the nose and throat area and the upper respiratory passages. This is to some extent also true of nicotine, the metabolism of which varies from individual to individual, and is mainly broken down into cotinine. The presence of nicotine and cotinine in body fluids confirms exposure to tobacco smoke. It is hardly possible to quantify the impact of tobacco smoke on the basis of the nicotine or cotinine concentration in body fluids. Such a procedure is hampered by the great difference between indoor tobacco smoke and mainstream cigarette smoke, the quick quantitative and qualitative changes to which indoor tobacco smoke is subject, the specific physico-chemical qualities of nicotine, and the individual differences in the metabolism of nicotine. Carbon monoxide and thiocyanate are further, but unspecific, markers for the absorption of tobacco smoke.

Epidemiological studied carried out so far and which point to a link between passive smoking and lung cancer as well as other diseases are tainted with so many errors - when critically considered - that they cannot be regarded as confirming any danger to health due to passive smoking. Problems in measuring exposure to tobacco smoke, in eliminating misleading factors such as misclassifications or 'confounders', and in the diagnosis and typification of lung cancers, have on the whole not been resolved. In the opinion of many scientists the epidemiological methods available to-day are probably inadequate to discern any risk to health through passive smoking, if indeed there is such a risk.

Since epidemiology has so clearly failed to establish whether there is a risk to health through passive smoking, it is not to be wondered at that by now toxicologists have taken the matter up. At present they are the strongest upholders of the theory of harmfulness to health, especially of the danger of cancer through passive smoking. They rightly assume that through passive smoking mutagenic and carcinogenic substances are inhaled, albeit in weak concentrations. They further assume, probably wrongly, that there is no threshold for cancerogenic substances, right down to the single molecule. These two assumptions together of necessity lead them to the conclusion that the risk of lung cancer - and probably of other cancers too - is increased through passive smoking, however small that increase may be. A linear extrapolation from tobacco-pollution through smoking to tobacco-pollution through passive smoking, which is made as a result of these assumptions and does not seem justified in the light of the known facts, leads to a similar assessment.

The question whether passive smoking causes lung cancer becomes the more of a political problem the more it is emotionalised in public discussion and the less science is able to provide an answer. For the present we can only say that danger to health is theoretically a possibility but has by no means been scientifically proved. Politicians interested in health affairs want to know whether a risk to health is probable. My answer would be "No", but I realise that we may yet have to wait a long time for the final word.

Literature can be obtained from the author.

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PASSIVE SMOKING AND LUNG CANCER: REANALYSES OF HIRAYAMAS DATA

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ABSTRACT

The cohort investigated by HIRAYAMA has a serve selection bias by age. The effect of removing this selection bias by iterative proportional fitting a contingency table to given marginals is investigated. The risk increase reported by HIRAYAMA disappears completely when one removes selection bias by age. If the cases would have been observed as they occur in the female population one would have observed no risk increase. Only in the subgroup of women married to industry workers there remains a risk increase, which might be due to confounding factors. Assuming modest differential misclassification also leads to risk ratios around unity.

INTRODUCTION

The statistical association between enviromental tobacco smoke and lung cancer is controversial. The HIRAYAMA study seems to provide sound epidemiological evidence supporting this hypothesis. In a recent paper ÜBERLA (6) has analysed the published studies. Regarding the HIRAYAMA study the following facts have to be kept in mind:

- The study was not designed to test the hypothesis, whether passive smoking is associated with lung cancer or not. It can therefore only generate this hypothesis, not prove it.
- The cohort was not representative for the population of Japan. A selection bias is possible.
- The exposure indicator - the fact of being married to a man who smokes - is not reliable, not valid and not specific.
- The event indicator - dying on lung cancer as noted on death certificates - is neither reliable nor valid.
- Various confounding factors - for instance exposure at the working place, indoor air pollution, overall air pollution, type of medical care - were not accounted for.
- Bias in registering the fact, that a woman is a nonsmoker, was not controlled. Resulting differential misclassifications of the cases, who were smokers and had to be excluded, have not been considered.
- Almost nothing is known about the 200 cases. No case reports are available, autopsy and histology are only available in 11.5 %.

The core of the information, on which the results of this study rely, is

1.) that during 1965 200 women in Japan told an interviewer on a single occasion that they were - during that time - non-smokers and their husbands told, that they were smokers, which might have been different before and afterwards and
2.) that their death certificates subsequently contained the diagnosis lung cancer, which might have been erroneous.

Such sparse information does not seem to be convincing.

In our paper we consider four questions:
1.) What is the relative risk when one removes the selection bias regarding age of women in the HIRAYAMA cohort?
2.) What is the relative risk when one additionally accounts for the fact that women above 70 who are married to busbands still living are less frequent than reported in the population statistic?
3.) What is the relative risk for women married to men with different occupations, when one removes the selection bias regarding age of men?
4.) What is the relative risk when additionally some modest differential misclassification is assumed?

MATERIALS AND METHODS

We start from tables 1, 2 and 3 of HIRAYAMA 1984 (4). These tables contain the most detailed published data. In order to check our program we reproduced some of the reported relative risks with good accuracy.

PERCENT FEMALE

AGE GROUP	JAPAN POPULATION	HIRAYAMA COHORT
40-49	39	42 ↑
50-59	30	35 ↑
60-69	19	22
70 +	12	1 ↓
	100	100

TABLE 1: Differences between the HIRAYAMA cohort and the female age distribution over 40 in the population of JAPAN 1965 (Population census 1965. Statistical survey of the economy of Japan. 1967, Ministry of Foreign Affairs of Japan).

There are marked differences between the HIRAYAMA cohort and the female age distribution over 40 in the population of Japan 1965. Women 50-59 are over-represented, women older than 70 are severely underrepresented. In this age group only one percent was observed instead of 12 percent in the population. The investigated cohort certainly has a severe selection bias by age, which needs no statistical test. This is likely due to the fact, that the smoking behaviour was not known in the elderly or that the husbands of older women have died. Since it takes twenty years and more from exposure to lung cancer, older women surely are relevant and should not be excluded. The majority of lung cancer cases occur in older age groups, in Germany more than 67 % in women over 65 years.

In order to answer the question what the relative risk is when the age selection bias is removed, we adjusted the data to the age distribution of the female population of Japan. The technique of iterative proportional fitting a contingency table to given marginals as described by BISHOP, FIENBERG and HOLLAND (1) or by HARTUNG (3) was used. This technique keeps the risks constant as observed in every cell and changes the marginals and the cell counts according to the given age distribution of the population. Iterative proportional fitting of contingency tables to given marginals is a well known technique in multivariate statistics and can be applied here without changing the observed interrelations between smoking habit, occupation and lung cancer. From the fitted or adjusted tables the risk ratios are calculated in the usual way. Such risk ratios based on data with removed age selection bias are the correct ones and should be used. One has to require that there should be no selection bias by age and the cases should be included as they would have occured in the population. Otherwise statistical tests and P-values are not very meaningful.

WIVES AGE	NON		HUSBAND'S SMOKING HABITS 1 - 19		20 +		TOTAL	
40-49	4	7918	21	17492	21	12615	46	38025
50-59	14	7635	46	15640	31	8814	91	32089
60-69	16	6170	31	10381	10	3793	57	20344
70 +	3	172	1	671	2	239	6	1082
TOTAL	37	21895	99	44184	64	25461	200	91540

TABLE 2: SMOKING HABIT OF HUSBAND BY AGE OF WIFE. ORIGINIAL DATA (Table 2 of HIRAYAMA 1984).

Table 2 shows the original data by age of wife. The cells contain the number of lung cancer cases and those under risk as published by HIRAYAMA. The 1-19 group includes ex-smokers in this and the following tables. 200 cases out of 91540 women were observed. Iterative proportional fitting to the female age distribution of the population leaves the underlined numbers constant. The others are adjusted using a rigth hand marginal which is made proportional to the age distribution of the population.

RESULTS

Table 3 gives the results of iterative proportional fitting to the female age distribution of the population. It contains the numbers of those under risk and of lung cancer deaths as they would have been ovserved, if HIRAYAMA had not excluded or preferred certain age groups. The age selection bias is removed. The risks in the individual cells are still the same as those observed by HIRAYAMA. Also the structure of the common distribution regarding age, smoking habit and lung cancer is unchanged. HIRAYAMA would have totally observed 232 cases instead of 200, with the corresponding numbers in the individual cells, had he included all women as they live in the population. This table is the best available starting point for age-adjusted risk ratio calculations. It was not used so far.

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WIVES AGE	NON		HUSBAND'S SMOKING HABITS 1 - 19		20 +		TOTAL	
40-49	3.91	7784.8	19.12	15927.8	20.02	12024.0	43.05	35700.6
50-59	12.49	6813.7	38.20	12987.1	26.95	7661.2	77.64	27462.0
60-69	14.25	5496.6	25.70	8604.9	8.68	3291.1	48.63	17392.6
70 +	32.02	1835.2	9.93	6664.2	20.79	2484.7	62.74	10984.8
TOTAL	62.67	21895	92.95	44184	76.44	25461	232.06	91540

TABLE 3: SMOKING HABIT OF HUSBAND BY AGE OF WIFE (Table 2 of HIRAYAMA 1984). Removed selection bias: Data adjusted to the age distribution of women in the population.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +
$\hat{RR}$	1.00	1.37	1.56
IL_{90}		1.00	1.11
MH-CHI		1.51	2.27
$P_{ONE\ TAILED}$		.065	.012*
$\hat{RR}$	1.00	.77	1.06
IL_{90}		.59	.80
MH-CHI		2.19	.27
$P_{ONE\ TAILED}$		.014**	.395

UPPER PART : STANDARDIZED BY AGE OF WOMEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF WOMEN

RR : Weighted point estimate of rate ratio
IL_{90} : Lower 90 percent confidence interval
* : "significant" in positive direction
** : "significant" in negative direction

TABLE 4: RELATIVE RISK BY AGE OF WOMEN (Calculated from table 2 of HIRAYAMA 1984)

In the upper part of table 4 one finds the risk ratios standardized by age only, as reported by HIRAYAMA. The lower part contains the risk ratios after removing the age selection bias. In the upper part the weighted point estimate of the rate ratio is 1.56 in the 20 + group and is technically "significant". IL_{90} designates the lower point of the 90-percent confidence interval in this and the following tables, as it was used by HIRAYAMA.

The risk increase disappears completely when one removes the selection bias by age. In the 20 + group the rate ratio is 1.06, hardly a relevant risk increase. In the group of 1-19 cigarettes per day it is .77 which is a technically significant risk decrease. The adjusted rate ratio, considering all those exposed in one group versus those not exposed is .81 with a confidence interval including unity. If HIRAYAMA had observed the cases as they occur in the population without selection bias by age, he would have observed no risk increase, but a sligth and meaningless risk decrease. This is the main result of our reanalysis, which corresponds well with the result of the prospective American cohort study as published by GARFINKEL (2).

In the discussion following our paper in TOKIO last november HIRAYAMA noted, that in the population the percentage of women over 70 married to men who are still alive is smaller than the percentage of women reported in the population statistics. Since we do not have the numbers we assume that only half of the women over 70 reported in the population census 1965 have been married to living husbands. The resulting hypothetical population together with the HIRAYAMA cohort is presented in table 5.

AGE GROUP	PERCENT FEMALE HYPOTHETIC POPULATION	HIRAYAMA COHORT
40-49	42	42 ↑
50-59	32	35
60-69	20	22
70 +	6	1 ↓
	100	100

TABLE 5: DIFFERENCES BETWEEN THE HIRAYAMA COHORT AND A HYPOTHETIC FEMALE AGE DISTRIBUTION OVER 40. (Explanation see text)

There is still possibly a selection bias in table 5. Now 6 percent of women over 70 would have been included in the hypothetic female distribution instead of 12 percent. The corresponding lung cancer cass, which generally are more frequent in this age group than in younger women, had been excluded. The reduction to one half accounts for the argument of HIRAYAMA mentioned above sufficiently. The resulting relative risks are presented in table 6. Even with these assumptions the relative risk is only 1.03 in the group of women married to husbands smoking 1-19 cigarettes per day, 1.29 in the 20 + group and 1.12 if one considers the smoking group altogether. All these risk ratios are not statistically different from unity.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +	SMOKER
$\hat{RR}$	1.00	1.03	1.29	1.12
IL_{90}		.77	.94	.85
MH-CHI		.05	1.33	.47

TABLE 6: RELATIVE RISK BY AGE OF WOMEN, AGE SELECTION BIAS REMOVED AND HYPOTHETICALLY ADJUSTED TO HIRAYAMAS ARGUMENT (see table 5)

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Since it is impossible for us to reconstruct the real situation some twenty years ago in Japan regarding the conditional distributions of males and females regarding age, smoking and family status, the reported results of the HIRAYAMA study can not be conclusive to us. As long as the selection bias by age can not be explained numerically in a sufficient way by HIRAYAMA, his thesis, that there is a significant and relevant risk increase based on his data migth as well be wrong.

We now consider two occupations, farmers and industry workers. From the upper part of table 7 one can see that the relative risk for wives of farmers seems substantial, when one standardizes by age of men only. The point estimates of the rate ratios are 1.48 and 1.63 respectively. This was observed earlier and had no adequate exlanation. If one removes the selection bias by age and adjusts to the male age distribution of Japan - the numbers in the lower part of table 7 - the rate ratios are .85 and .82, not different from unity. This seems more plausible.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +
$\hat{RR}$	1.00	1.48	1.63
IL_{90}		.97	1.01
MH-CHI		1.48	1.92
$P_{ONE\ TAILED}$		.069	.027
$\hat{RR}$	1.00	.85	.82
IL_{90}		.59	.53
MH-CHI		.42	.53
$P_{ONE\ TAILED}$		.337	.296

UPPER PART : STANDARDIZED BY AGE OF MEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF MEN

TABLE 7: RELATIVE RISKS: WIVES OF FARMERS ONLY
(Table 3 of HIRAYAMA 1984)

Considering the wives of industry workers only, in the upper part of table 8 the point estimates of the rate ratios are 1.77 and 2.27, standardized by age of men, being not significant. Removing the age selection bias - in the lower part of table 8 - there is a remarkable risk increase to 4.60 and 6.90, which is significant. However, there are only 9 lung cancer deaths in the 20+ group and only 3 in women 70 years and older, which are small numbers, but these are numbers observed and used by HIRAYAMA and his risk structure is unchanged. Thus only in the subgroup of women married to industry workers there is a risk increase, in all other occupations there is no risk increase. Omitting industry workers, the point estimates of the rate ratios are .90 and .89, not significantly different from unity. These findings are consistent with the assumption of confounding factors in women married to industry workers, who migth be exposed to other enviromental hazards. Our calculations show that by removing age selection bias by age, one can explain hitherto implausible results.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +
$\hat{RR}$	1.00	1.77	2.27
IL_{90}		.70	.84
MH-CHI		.73	.81
$P_{ONE\ TAILED}$		.232	.208
$\hat{RR}$	1.00	4.60	6.90
IL_{90}		1.71	2.45
MH-CHI		2.50	2.78
$P_{ONE\ TAILED}$		.006	.003

UPPER PART : STANDARDIZED BY AGE OF MEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF MEN

TABLE 8: RELATIVE RISKS: WIVES OF INDUSTRY WORKERS ONLY
(Table 3 of HIRAYAMA 1984)

Active smoking is correlated among married couples. In a society in which female smokers were very rare in 1965, more women married to smokers will declare themselves nonsmokers than the other way round. One has therefore to consider biased or differential misclassification. There are likely more women with lung cancer, who have been misclassified as nonsmokers than the other way round. They have to be removed from the cohort. We made some moderate assumptions regarding misclassification, as shown in table 9. In order to examine, how sensitive the relative risk is we removed 10, 20 and 30 cases from the exposed groups corresponding to 5, 10 and 15 percent. Assuming 30 misclassified cases - 15 percent, a percentage which has been observed in the literature (5) - the rate ratios are .66 and .85. In the group 1-19 cigarettes per day all the risk estimators are significantly smaller than unity. Our personal opinion is that 10 differential misclassified cases from 200 is a fair number. The corresponding weigthed point estimates of the rate ratio are .74 and 1.00. These risk estimates are as reasonable as other risk estimates calculated from the HIRAYAMA data. They indicate - if anything - a risk decrease, not a risk increase.

NUMBER OF CASES ASSUMED MISCLASSIFIED AND REMOVED FROM EXPOSED GROUPS		HUSBAND'S SMOKING HABITS NON	1-19	20 +
n = 10 = 5 %	$\hat{RR}$	1.00	.74	1.00
	$P_{ONE\ TAILED}$		.006	.469
n = 20 = 10 %	$\hat{RR}$	1.00	.70	.93
	$P_{ONE\ TAILED}$		.003	.383
n = 30 = 15 %	$\hat{RR}$	1.00	.66	.85
	$P_{ONE\ TAILED}$		.001	.238

TABLE 9: RELATIVE RISK: ASSUMED DIFFERENTIAL MISCLASSIFICATION
(Age selection bias removed and standardized by age of women)

DISCUSSION

Reanalyses of data, which have been collected by others are not easy. This is because information is not completely available, because information might be misinterpreted or because one has to take another view in order to come closer to the acceptable truth. Our calculations do not diminish the great value and impact the HIRAYAMA study had on the epidemiology of passive smoking. They show however, that reasonable alternative views on the same data are possible, which lead to opposite conclusions. Our findings are in contrast to HIRAYAMA's thesis that - based on his data - there is a substantiall statistical association between passive smoking and lung cancer. We do not hold that our view is the only correct one. We do hold however, that the risk ratios calculated by us, removing age selection bias, are as reasonable as the ones calculated by HIRAYAMA. Since they go back to the population and not to a selected sample our estimates could be preferable. Hypothetically accounting for the argument of HIRAYAMA, that in the population the percentage of women over 70 married to men who are still alive is smaller than the percentage of women reported in the population statistics does not change our results. Our risk estimates are a consequence of the data published by HIRAYAMA and can not be rejected from the study data, as they are published so far.

		HUSBAND'S SMOKING HABITS NON	1-19	20 +
AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (WOMEN)	$\hat{RR}$	1.00	.77	1.06
	$P_{ONE\ TAILED}$		.014	.395
WITHOUT INDUSTRY WORKERS, AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (MEN)	$\hat{RR}$	1.00	.90	.89
	$P_{ONE\ TAILED}$		.394	.179
10 CASES ASSUMED MISCLASSIFIED, AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (WOMEN)	$\hat{RR}$	1.00	.74	1.00
	$P_{ONE\ TAILED}$		.006	.469

TABLE 10: REANALYSIS OF HIRAYAMAS DATA: SUMMARY OF RELATIVE RISKS

To summarize: Removing the age selection bias in the HIRAYAMA study one gets a relative risk of 1.06 in the group of women married to men with more than 20 cigarettes per day. In the group of women married to men with 1-19 cigarettes per day the relative risk is .77, a technically "significant" risk decrease. If HIRAYAMA could have observed the lung cancer cases as they occur in the female population, he would have observed no risk increase, but a risk decrease to around .81, not significantly different from unity, considering those exposed versus those not exposed.

If one omits the wives married to industry workers because of possible confounding factors the relative risk is .90 and .89 respectively. This is of the same size order and smaller than unity. Here we could adjust and standardize by occupation and age of men only, which is not as appropriate as by age of women.

If one assumes that 10 cases are differentially misclassified and removes them from the exposed groups, the risk estimates are .74 and 1.00 respectively.

Our findings demonstrate how sensitive the data of this study are and how week the evidence for a statistical association between passive smoking and lung cancer from this study is. In view of these and other facts, which we mentioned in the introduction, the null hypothesis might be true as well and is consistent with the HIRAYAMA data in the same way as the alternative hypothesis.

We would be glad to apply our technique to more detailed data if we can get them from HIRAYAMA, for instance in order to adjust by occupation of men and age of women, or by occupation of men and by age of women married to a husband who is still alive. We are ready to modify our view if such data can support the alternative hypothesis better than the published data do. We do hope, that our calculations give rise to a fruitful discussion. The methods we used here might be of interest to the analysis of other cohort and control studies.

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Meta-Analyses on Passive Smoking and Lung Cancer

H. Letzel and K. Überla

Summary

Up to now, meta-analysis has rarely been used in epidemiology and no generally accepted standards are available. Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers.

In our paper two cohort and ten case-control studies were analyzed using several statistical techniques (Fisher, Mantel-Haenszel, Yusuf). Only data from women were included and a quality indicator (histology exposure, methodology) was used to analyze different study combinations, i.e. an analysis of sensitivity was performed. For the Hirayama study two different risk estimates were used. In addition, all 1,023 logically possible combinations of the 10 case-control studies were analyzed.

Of all possible meta-analyses of the 10 case-control studies, 670 (65.5%) were not significant at $P \leq 0.05$ (Yusuf technique). The Trichopoulos study is involved in 330 of the 353 significant study combinations, indicating that this is the dominating case-control study, although the methodological quality is unacceptable.

Combining case-control and cohort studies, the relative risk estimates range from 1.013 to 1.118, depending on the specific subset of studies analyzed. These relative risk estimates include unity. The quality of the individual studies is highly variable and sometimes poor. We conclude that as long as no better studies are available, meta-analyses cannot and do not add much new evidence to the question of whether passive smoking is related to lung cancer.

Up to now, meta-analyses have mainly been used with randomized clinical trials. The technique has been criticized [6, 10, 23] for various reasons. Standards for meta-analyses in epidemiology are not yet available. Bias by non-reporting of studies, by selecting certain subgroups or by redefining sample sizes can create additional difficulties for a statistical evaluation. How different study designs – e.g. case-control versus cohort studies – should be weighted is left to the investigator. It is not surprising that the application of such methods in a controversial field like passive smoking and lung cancer does not come up with uniform results.

The inclusion of studies in meta-analyses is justified as long as there are no major methodological shortcomings in the individual studies. Combining biased or confounded results by meta-analysis cannot provide correct answers. There is a strong case for an analysis of sensitivity [23]. It investigates the effect of different study selections as well as the impact of different statistical methods on the results.

When the first papers on passive smoking and lung cancer were published a serious hypothesis was created [11, 27]. This hypothesis is serious because – if it is right – thousands of non-smokers are being killed worldwide by smokers. But the hypothesis is also serious because – if it is wrong – smokers are being accused of killing other people without actually doing so.

H. Kasuga (Ed.) Indoor Air Quality

Last year Wald [31] published the first meta-analysis of the available studies on passive smoking and lung cancer. In his paper the results obtained in men were included, and in two studies the subgroup of women married to ex-smokers was excluded. The quality of the individual studies was not taken into account and no analysis of sensitivity was performed.

Every meta-analysis has to state its goals, criteria and methods before it starts. In our analysis we planned

1) to include only studies which fulfil minimal methodological requirements. We wanted to eliminate statistical noise.
2) to select carefully the "best" relative risk estimate from every study, not just the one which was reported by the authors or the highest one.
3) to classify the quality of the studies regarding determination of histology, estimation of exposure and overall study methodology.
4) to use different statistical techniques, namely the Fisher method and the method used by Yusuf [32] or Wald [31].
5) to study the sensitivity of the results with regard to including different subsets of studies depending on their qualities.

Selection of Studies

We did not include the studies by Gillis [9], Knoth [16], Miller [22] and Sandler [24–26]. These studies do not fulfil minimal methodological criteria and they do not contain relevant information. Only insufficient data are available from them. Wald [31] had included the Gillis study [9], which only has 14 non-smoking lung cancer cases and correspondingly wide confidence intervals contributing nothing to the available evidence.

We also excluded men because the majority of evidence comes from studies in women. Only about 11% of the reported cases are men. Their results vary widely. There is not a single significant result in men. The situation regarding biology, exposure and reporting habits is considerably different in men as compared to women.

We included two cohort studies [7, 12–14] and 10 case-control studies [1–5, 8, 15, 17, 19–21, 27, 28]. These studies had also been included by Wald [31]. The only difference is that we didn't include the Gillis study [9] and that we restricted our analysis to women. The availability of histology, the quality of the exposure indicator and an overall quality rating of the study were judged by K. Überla. Three study groups resulted: cohort studies, case-control studies with reasonable quality (quality +) and case-control studies with poor quality (quality −) (Table 1).

The 2 × 2 tables and RR estimates for the 12 studies used are presented in Table 2. Generally, these numbers are the same as used by Wald [31] with the exception that we did not exclude the wives of ex-smokers in the studies by Hirayama [14], Trichopoulos [27, 28] and Koo [17].

Regarding the Hirayama study we did not use a relative risk estimate of 1.63 as did Wald [31]. In a subsequent paper by Überla and Ahlborn [30], which will be presented in this session of the conference, it is shown that, when one adjusts the Hirayama cohort to the age of the female population in Japan, the relative risk is 0.90. We alternatively used a risk estimate of 1.45 for the Hirayama study. This was calculated from Table 2 of the 1984 publication by Hirayama [13] and was standardized by the age of women only.

Table 1. Quality rating of studies selected for meta-analyses

Author	Histology	Exposure	Quality rating**	Resulting group
Hirayama	–*	–	3	Cohort
Garfinkel	–	–	2	Cohort
Chan et al.	+	+	4	CC quality +
Correa et al.	–	–	5	CC quality –
Trichopoulos et al.	–	–	6	CC quality –
Buffler et al.	+	–	4	CC quality +
Kabat et al.	+	+	4	CC quality +
Garfinkel et al.	+	+	4	CC quality +
Akiba et al.	–	–	5	CC quality –
Lee et al.	–	+	5	CC quality –
Koo et al.	+	+	4	CC quality +
Pershagen et al.	+	+	4	CC quality +

The included studies are the same as in the paper by Wald et al. (1986). We included women only.
** 2 = acceptable; 3 = possibly flawed; 4 = bias and confounding suspected; 5 = major bias and confounding suspected; 6 = unacceptable

Table 2. 2 × 2 Tables and relative risk estimates for studies selected for meta-analyses

Author	Exposed lung cancer		Unexposed lung cancer		Relative risk
	+	–	+	–	
Hirayama	163	69,428	37	21,858	1.45 (1) 0.90 (2)
Garfinkel	88	127,164	65	49,422	1.18
Chan et al.	34	66	50	73	0.75
Correa et al.	14	61	8	72	2.03
Trichopoulos et al.	53	116	24	109	2.01
Buffler et al.	33	164	8	32	0.80
Kabath et al.	13	15	11	10	0.79
Garfinkel et al.	91	254	43	148	1.23
Akiba et al.	73	188	21	82	1.48
Lee et al.	22	45	10	21	1.03
Koo et al.	66	97	22	40	
Pershagen et al.	33	150	34	197	1.27

The underlined numbers are different from those assumed by Wald. We did not exclude the wives of ex-smokers.
(1) Hirayama standardized by age of women only (from Table 2, Hirayama 1984)
(2) Hirayama with age selection bias removed (Überla and Ahlborn, 1987)

Results

Meta-Analyses for All Possible Case-Control Study Combinations

In order to get a feeling for the consequences of random selection of studies, we first considered all possible combinations of case-control studies. With 10 case-control studies there are 1,023 possible study combinations or subsets for which a meta-analysis can be performed. We calculated them all. The results can be summarized as follows:

34.5% of all possible meta-analyses - using the Yusuf technique - are technically significant at $p \leqq 0.05$. That means that a random selection of studies leads to a probability of 65.5% for a negative result of the meta-analysis.

The Trichopoulos study is involved in 330 of the 353 significant study combinations, that is in 93.5%. This study is the dominant study in the significant combinations. Without the Trichopoulos study only 23 out of the 511 then possible study combinations are "significant", that is 4.5%. One has a probability of 95.5% for a negative result selecting a subset of studies for a meta-analysis randomly.

The Trichopoulos study was judged as methodologically unacceptable. It is a textbook example of how a case-control study should not be performed [29]. If it were included, however, the impact of this study on the results would prove to be heavy.

Table 3. Results of meta-analyses I

Author		Cohort only	Case-control quality +	Case-control quality −	Cohort plus CC quality +	All
Hirayama*		×			×	×
Garfinkel		×			×	×
Chan			×		×	×
Correa				×		×
Trichopoulos				×		×
Buffler			×		×	×
Kabath			×		×	×
Garfinkel			×		×	×
Akiba				×		×
Lee				×		×
Koo			×		×	×
Pershagen			×		×	×
Fisher:	p	0.017	0.604	0.007	0.137	0.009
Yusuf:	$\widehat{RR}$	1.271	1.074	1.652	1.178	1.260
	IL 95	1.025	0.848	1.201	1.005	1.093
	IU 95	1.575	1.361	2.272	1.381	1.453
	p**	0.014	0.277	0.001	0.022	0.001

* Hirayama standardized by age of women only, RR = 1.45 as calculated from Table 2, Hirayama, 1984
** one-tailed

Table 4. Results of meta-analyses II

Author		Cohort only	Cohort plus CC quality +	All without Trichopoulos	All
Hirayama adjusted*		×	×	×	×
Garfinkel		×	×	×	×
Chan			×	×	×
Correa			–	×	×
Trichopoulos			–	–	×
Buffler			×	×	×
Kabath			×	×	×
Garfinkel			×	×	×
Akiba			–	×	×
Lee			–	×	×
Koo			×	×	×
Pershagen			×	×	×
Fisher:	p	0.105	0.336	0.158	0.028
Yusuf:	$\widehat{RR}$	1.013	1.035	1.076	1.118
	IL 95	0.848	0.941	0.941	1.273
	IU 95	1.210	1.193	1.230	1.299
	p**	0.443	0.317	0.142	0.046

* With age selection bias removed. RR = 0.902 (Überla and Ahlborn 1987)

** one-tailed

Meta-Analyses for Selected Study Groups

Meta-analyses for various combinations of cohort and case-control studies were calculated. The results are given in Table 3. For the Hirayama study a relative risk of 1.45 for the exposed versus non-exposed persons is used in all these combinations as one of the starting points. The results show that the probability using the Fisher method is always higher than the probability using the procedure as applied by Yusuf [32] or Wald [31]. This had to be expected. The other methods – Mantel-Haenzsel or for the cohort studies risk ratios – do not differ much from the Yusuf method. All the study combinations on Table 3 are significant with the exception of the reasonable quality case-control studies. These six studies have a common risk estimate of 1.07, being not statistically different from unity.

The meta-analyses for these study combinations were repeated using a relative risk of 0.90 for the Hirayama study as was calculated by Überla and Ahlborn [30]. The pooled risk estimates are very close to unity and are not statistically significant (Table 4). When one includes the Trichopoulos study, the pooled estimate for the relative risk is 1.118, approaching but not reaching statistical significance.

Discussion

To summarize, the expected overall risk of dying of lung cancer for non-smoking women married to smoking men is:

- 1.074 out of six case-control studies of reasonable quality,
- 1.013 out of two prospective studies, using the Hirayama study with the age selection bias removed as shown by Überla and Ahlborn,
- 1.035 out of two prospective studies and six case-control studies of reasonable quality,
- 1.076 out of eleven studies, with the Trichopoulos study excluded, and
- 1.118 out of all twelve studies including the Trichopoulos study.

These risk estimates are not statistically different from unity.

Thus, the overall result of various meta-analyses can be summarized as follows: Meta-analysis of 12 relevant studies (using women only and adjusting the relative risk of Hirayama for age selection bias) gives an overall estimate of relative risk of dying of lung cancer for non-smoking women married to smoking men of $\widehat{RR} = 1.076$ (Trichopoulos excluded) or $\widehat{RR} = 1.118$ (Trichopoulos included). These risk increases of about 8% or 12% are not significantly different from unity.

Our results differ widely from the results given by Wald [31]. The main reasons are different relative risk estimates for the individual studies. The papers by Hirayama and Trichopoulos were the first studies to be published on this issue. All later studies give less indicative results. Whether wives of ex-smokers should be included or not, whether the Hirayama study has to be adjusted for age selection bias and whether the Trichopoulos study is methodologically as stringent as a case-control study should be is open for discussion and will be answered differently by individual scientists. We have shown a variety of possible outcomes of meta-analyses and demonstrated the sensitivity of the results with varying assumptions.

The whole question of meta-analyses comes down to the question of the quality of the individual study. As long as there are no better studies available, meta-analyses cannot and do not add much new evidence to the question whether passive smoking is related to lung cancer.

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Review article

Lung cancer from passive smoking: hypothesis or convincing evidence?

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Summary. The epidemiological literature on passive smoking and lung cancer is reviewed and the well-known criteria for establishing a causal relationship are applied in order to determine what level of causal evidence currently exists. Three cohort studies and 12 case control studies are analysed. Of the prospective cohort studies, one contributes very little to our knowledge, one shows no risk increase and one results in a moderate risk increase of 1.74 for women married to heavy smokers. The last is the only study which has to be taken seriously, even when other considerations show that its results might be caused by chance, bias or confounding. None of the six case control studies yielding a positive relationship was conducted according to the state of art of epidemiological research, giving reasonable and sound evidence which cannot be explained by chance, bias, confounding or misclassification. Two studies contribute nothing to the evidence. None of the four case control studies yielding no risk change or a risk decrease can exclude the possibility that a causal relation exists. The epidemiological and toxicological evidence is discussed in the light of recent findings. The volume of accumulated data is conflicting and inconclusive. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk. Applying the criteria proposed by IARC there is a state of inadequate evidence. The available studies, while showing some evidence of association, do not exclude chance, bias or confounding. They provide, however, a serious hypothesis. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

Key words: Passive smoking – Lung cancer – Causal connection

Introduction

Active smoking is the most important, avoidable health hazard in industrialized countries. If passive smoking causes lung cancer, this would be a very strong argument against active smoking. It could be the decisive argument for reducing active smoking considerably. Science should determine whether this hypothesis is true or not. If it is to do so, one must seek to state the facts and to separate these from mere speculation.

There are eight well established criteria which should be fulfilled if a causal connection in epidemiology is to be inferred:

- *Consistency* of the association in various studies. The results should be reproducible in similar circumstances.
- *Strength and intensity* of the association. Risk ratios of 5, 10 or greater are more likely to indicate a causal relationship than a risk ratio of around 2.
- *Specificity* of the association. The exposure, the effect and the way in which the exposure works should be specific. Therefore exposure and effects should be measured with sufficient validity and specificity.
- There should be a *dose-response relationship*.
- *Exclusion of bias and confounding factors*.
- There should be *statistical significance*.
- *Impact of intervention*, i.e. there should be studies showing a decrease of the effect when the exposition has been diminished.
- There should be *biological plausibility*.

Taking these criteria into consideration, the IARC has proposed four different levels of evidence [22] when evaluating the existence of a causal relationship regarding carcinogenicity in humans:

(1) Sufficient evidence of carcinogenicity: There is a causal relationship between the exposure and human cancer.
(2) Limited evidence of carcinogenicity: A causal interpretation is credible, however, alternative explanations (such as chance, bias, confounding) cannot adequately be excluded.
(3) Inadequate evidence: There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
(4) No evidence: Several adequate studies are available which do not show evidence of carcinogenicity.

In this article the available literature is examined in light of the criteria required to infer a causal connection and thus to determine what IARC level of causal evidence currently exists.

Cohort studies

Adequate and well conducted cohort studies can provide sound, empirical evidence on a causal relationship between exposure and event. To date, three cohort studies on passive smoking (from Hirayama, Garfinkel and Gillis et al.) have been published.

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Evidence from this study has been published in four reports [18, 19, 20, 21]. In addition there are several critical comments [4, 24, 32, 33, 34, 37, 38, 47, 48, 49, 54, 60]. Married, nonsmoking women aged 40 and above ($n = 91540$) from a cohort of 265118 adults in 29 health center districts in Japan were followed for 15 years. Altogether, 200 women died of lung cancer. Standardized mortality rates for lung cancer were calculated according to the smoking habits of the husbands. The point estimate of the rate ratio was 1.74 or 1.79 when comparing women of nonsmoking husbands to women whose husbands smoked more than 20 cigarettes per day. There was a dose-response relationship which was also significant. Standardization using the age of women and the occupation of husbands was performed. In nonsmoking men with smoking wives, seven lung cancer deaths occurred, resulting also in a relative risk of around 2.

In evaluating the results of this study the following points must be taken in consideration:

(1) The study was designed to screen for a wide variety of possible risk factors on life events and not to test the hypothesis that passive smoking causes lung cancer. It therefore cannot prove this hypothesis, but rather can only generate it. The hypothesis that passive smoking causes lung cancer is one of several secondary hypotheses which can be extracted from this material.

(2) The reported cohort is not representative of the population of Japan. The age distribution of females over 40 in Japan in 1965 was different from the age distribution in the cohort [44]. Of 265118 adults (122261 men and 142857 women) only 91540 nonsmoking married women, whose husbands smoking habits were known, were included in the study. 51317 women (35.9%) were not used, partly because the smoking habits of the husbands were not known and the corresponding 103 nonsmoking lung cancer cases were not entered in the study. Even when most of them were not married, some selection mechanism was at work. The precise effect of this selection, for instance, regarding occupation of wives, is unpublished and unknown.

(3) The indicator, by which the exposure to passive smoking was estimated, was neither specific nor was its reliability or validity assessed [24]. The state for a woman "being a nonsmoker and being married to a man who smokes a certain number of cigarettes" was registered once in 1965. The duration of this status is unknown and was not accounted for. A woman living with a smoker in 1965 for a year and then dying of lung cancer was treated as married to a smoker in the same way as a woman being a passive smoker for 30 years. A woman, who began smoking a year after the start of the study and who died of lung cancer, was treated as a nonsmoker. The exposure to sidestream smoke in the working place for women – approximately 45% for men and 25% for women of the total exposure in Germany [40] – is not contained in the indicator. Being married to a man who smokes might mean a lot of other risks influencing the cause of death, for instance risks from food, environment, social conditions, living in cities or in villages, size of living space at home, or occupation of the women. The selection of partners will most certainly introduce some other risk factors which have not been

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accounted for. It has been shown that being married to a man who smokes is consistent with a wide variety of exposure to sidestream smoke [11, 39, 59]. One study [11] shows, that 40 to 50% of persons with nonsmoking spouses reported some passive exposure and conversely 30 to 35% who were married to smokers reported no exposure. The concordance on directly and indirectly reported smoking habits of the spouse was 85% in another study [36]. Being married to a man who smokes is not a valid and accurate indicator of the extent to which one is exposed to passive smoking and is by no means specific.

(4) The event – dying from lung cancer – was not assessed in a way which corresponds to the state of the art. It is well known that the causes of death on death certificates disagree to a certain extent with the real cause of death. It is safe to assume that at least 10% have died from causes other than those specified on the death certificate. In one study [13], the cause of death on death certificates was not confirmed by the treating physician in 16.7% of the lung cancer cases. An autopsy was available from only 23 (11.5%) of the 200 cases. However, the histological type of lung cancer is decisive in establishing a causal connection. Women frequently have adenocarcinomas, a histological diagnosis that is not believed to be connected to smoking as strongly as squamous or small cell carcinoma. Neither the exposure nor the event were assessed or monitored in a way approaching the standards which are applied in other fields of risk evaluation, for instance in studies on adverse drug reactions.

(5) Various confounding factors were not adequately considered in this study; for instance, exposure to other substances in the working place, (dust, fumes or vapours), overall air pollution, exposure to indoor pollution, such as kerosene stoves, genetic condition, food, type of medical care and others.

(6) Bias in registering the fact that a woman was a nonsmoker, was neither controlled for nor excluded. Some women who were active smokers might have declared themselves nonsmokers in a society where smoking women were not well accepted and who made up an absolute minority. Such women developing lung cancer will then be included as cases.

(7) The percentage of possible misclassifications and its likely effect on the results have not been examined. With a certain percentage of misclassifications in the category "nonsmoking women" among the lung cancer cases, the statistical differences will disappear. Recent studies [26, 35] have shown that misclassification can easily explain the association between lung cancer and passive smoking in case control studies.

(8) Almost nothing was reported on the 200 cases. There are no case reports available, from which individual histories can be judged or at least partly evaluated regarding other relevant factors. This is standard in other areas, e.g. the evaluation of rare adverse side effects from drugs. The core of evidence we have on the cases is that, during 1965, 200 women in Japan told an interviewer on a single occasion that they were, at that time, nonsmokers, married to a smoker and their death certificate subsequently contained

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(9) The trend in lung cancer rates in Japan between 1950 and 1979 was over nine-fold in men and over six-fold in women [31]. This risk increase cannot be explained by passive smoking. Comparing the total population to that of nonsmokers from Hirayama's own data, this ratio is only four-fold in men and just under two-fold in women. This indicates that there might be some other important cause of lung cancer which was not studied.

(10) Some statistical arguments have to be kept in mind: Nobody knows how many tests have been applied to this material. Adjustments for multiple tests, however, would considerably reduce significance levels. Statistical tests with huge numbers in the denominator are not as convincing as the accompanying small type I error indicates. The larger the number and the smaller the incidence, the more important are bias and confounding. For very small incidences, the theoretical models are not very appropriate. Diamond and Forrester [10], using a Bayesian approach, have shown how small the posterior probability for Hirayama's hypothesis could be. Using their analysis, Hirayama's results could well be consistent with the null hypothesis. The statistical significance of Hirayama's risk ratios could be a matter of chance or an artifact induced by some of the many problems occurring in such a large study.

Considering all these arguments, the study at best suggests the hypothesis of a causal association. Still, the null hypothesis might also be true. Even when a dose-response relationship seems to exist in this study, chance, bias or confounding factors could as adequately explain the results as does the hypothesis that passive smoking causes lung cancer.

Garfinkel

This re-analysis [13] uses data from the ACS-study [12] and from the Dorn study [57] in the USA. Nonsmoking women (n = 176, 739) married to men with known smoking habits were included. The period from 1955–1972 was covered. The relative risk adjusted for several factors was 1.04 when women married to nonsmokers were compared to women married to husbands smoking more than 20 cigarettes per day. There was no statistical significance and no dose-response relationship. The authors argue that if passive smoking is of practical importance, then there should be an increase in death rates due to lung cancer among nonsmokers. This could not be found.

The sample size and the level of details of this study are comparable to Hirayama's material. Some information, for instance on histology, is more specific. There is, however, no indication of a statistical connection between passive smoking and lung cancer. The paper failed to reproduce the Hirayama results and did not add evidence to this hypothesis. If there is a relevant increase in lung cancer risk from passive smoking, it should also have shown up in Garfinkel's study. The Garfinkel study does not of course disprove the Hirayama hypothesis.

Gillis et al.

This study was published in 1984 [15] and presents only very few cases (6 men and 8 women) with lung cancer among nonsmokers. It does not show any trend or statistical significance because of these small numbers. This study contributes very little to the empirical evidence in either direction.

Summarizing the evidence from cohort studies, the conclusion is that only the Hirayama study, which has severe drawbacks, provides any empirical evidence in favour of the hypothesis that passive smoking may cause lung cancer in nonsmokers.

Case-control studies

In assessing the relative risk of rare events, case control studies can provide valuable information by estimating odds ratios. Such studies cannot prove a causal connection. They can, however, give sound empirical evidence, provided several studies have consistently similar results, the effect and the event are determined with some validity, the odds ratios are large and bias can be adequately excluded. Twelve case-control studies have been published so far on the relationship between passive smoking and lung cancer.

Trichopoulos et al.

In this study [55,56], 77 nonsmoking women with lung cancer and 225 nonsmoking women with other diseases were compared with regard to the smoking habits of their husbands. The authors calculated an odds ratio of 2.4 and 3.4 when comparing women married to nonsmokers with women married to men who smoke less than one pack of cigarettes per day and more than one pack per day respectively. The linear trend of these ratios is significant. The authors were aware of some of the limitations of this study and concluded that further investigations were warranted.

The Trichopoulos study is a textbook example for some of the errors which must be avoided if a case-control study is to be valid:

— The cases are from three cancer hospitals, the controls from a hospital for orthopedic disorders. A systematic bias is therefore likely.
— An interviewer bias must be expected: the same medical doctor selected the controls and interviewed them. He was fully aware of the goal of the study.
— A bias in recalling the passive smoking history is likely in patients. At least some of the cases knew their diagnosis, whereas the controls were not aware of a life-threatening disease.
— Patients with adenocarcinoma and with alveolar carcinoma were excluded, so that there was a selection among the lung cancer cases. This makes it a study of a subset of lung cancer more associated with active smoking.
— The histological type of lung cancer is not available in 35% of the cases.
— In assessing the exposure, there is no specificity and no validity. Misclassification might have occurred [26,35]. Being married to a cigarette smoker

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may not be a valid indicator of exposure to passive smoking and could indicate various other risks.

– Confounding factors, such as exposure at the work place, food, etc. were not considered.
– The calculated odds ratios are incorrect, they should be 1.95 and 2.54 [16].
– The risk of active smoking is on the same size order as that of passive smoking, a result that is biologically implausible.

The total number of cases is small. The statistically "significant" results of this study might well be artifacts from chance, bias or confounding. The study provides no valid evidence for a causal connection of passive smoking and lung cancer.

Correa et al.

Lung cancer patients ($n = 1338$) from a large number of hospitals in Louisiana were compared to 1393 controls from the same hospitals with regard to the smoking habits of spouses and parents [7, 8]. Eight male nonsmokers (from 1036) and 22 women nonsmokers (from 302) could be used for calculating odds ratios with regard to passive smoking.

The exposure was estimated in total lifetime pack-years by interviewing patients or their next of kin. Women married to smokers with more than 40 pack-years had an odds ratio of 3.52, which was significant ($P \leq 0.05$). Various other odds ratios were calculated but were within chance limits. The authors concluded that the similarity of their findings with those of Trichopoulos strengthened the suspicion that passive smoking may contribute to lung cancer. The study also revealed a relative risk of 1.66 for patients whose mothers smoked and of 1.04 if the father was a smoker. The relative risk for patients whose mother smoked decreased to 1.36 when one takes into account the active smoking of the subject. The effect of maternal smoking is only significant in males. How maternal smoking causes lung cancer in males, but not in females, can only be a matter of speculation according to the authors.

The numbers of nonsmoking cases are small. Misclassification could be a sufficient explanation for the association. In view of the many calculated odds ratios, one single ratio reaching $P \leq 0.05$ is not surprising. There might be a selection bias. 76% of the cases and 89% of the controls were interviewed by professional interviewers. It was not mentioned which percentage of the patients themselves and which percentage of the next of kin gave the information. This might be different in cases and controls. The inconsistencies in this publication can most easily be explained by the large number of odds ratios calculated from very few nonsmoking cases, by possible bias, by chance, or by confounding factors. The study does not provide convincing evidence for a causal relation between passive smoking and lung cancer.

Sandler et al.

The authors published three reports from the same data base [50, 51, 52], covering in the first paper the effect of smoking of the spouse, in the second

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paper the combined effect of father, mother and spouse, and in the third paper only the childhood exposure. Several critical comments have been published [5, 17]. Cancer cases from all sites ($n = 518$) were compared to 518 controls in the first paper, and an odds ratio of 1.6 for all cancer sites and one of 1.6 for lung cancer was reported.

These results are not very meaningful for a variety of reasons. Controls were selected by cases in 60%. The cases answered questions on smoking, knowing that they had cancer and that there is a relation between smoking and cancer. They proposed friends without cancer to answer questions on smoking, thereby possibly selecting friends with less exposure to smoke. The level of education differs significantly between cases and controls together with other confounding variables connected with education. The reporting was not comparable between cases and controls: the number of missing values on marital status and occupation are different and the same might have been the case in reporting on passive smoking. The results are not presented by age and sex of the nonsmokers, so that details of the calculations cannot be verified. Combining all types of cancer with different etiology and epidemiology does not make biological sense. The crude odds ratio for smoking is much smaller than the one for passive smoking, which is biologically implausible. The authors claim that passive smoking is related to a number of cancers not related to active smoking, which is not plausible, because active smokers are more exposed to sidestream smoke than nonsmokers. There was no clearcut dose-response relationship. Exposure outside the home was disregarded. Misclassification could explain part or all of the results. The evidence for lung cancer is especially weak: there were only 22 cases reported, 20 of them smokers, so that the whole evidence on passive smoking and lung cancer in this study is based on two nonsmoking lung cancer cases.

In the second and third papers, there is no further serious evidence on lung cancer caused by passive smoking. A large number of odds ratios and error probabilities is calculated, based essentially on the same two nonsmoking cases as in the first paper. Adjusting for multiple factors can add nothing to the evidence in such a case. There are at best hypotheses generated, most of which will not be reproducible in further studies.

Chan and Fung

In this paper [6], 84 female nonsmoking lung cancer patients were compared to 139 controls regarding the smoking habits of spouses. The authors gave the numbers, but did not calculate the odds ratio, which is 0.75 and within chance limits. This study – giving the histological type of tumor and some information on cooking habits – does not support the hypothesis that passive smoking causes lung cancer.

Koo et al.

Koo et al. have presented three papers on the subject [28, 29, 30], giving an analysis of risk factors in 1781 lung cancer cases from Hongkong in the first. Since it is not evident from the second and third papers whether they refer at

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least partially to the same cases, only the second paper with 200 cases and 200 controls is considered here. The third paper with 120 cases and 120 controls had very similar results.

Two hundred female lung cancer cases were compared with 200 female controls regarding the exposure to passive smoking. Eighty-eight cases and 137 controls had never smoked (66 and 97 with passive smoke exposure, odds ratio 1.24) and 112 cases and 63 controls had smoked. The histological diagnosis is provided for all cases. A very detailed interview of all cases and controls was conducted by trained interviewers. The information on the patients and controls is more detailed than in all other studies. The exposure to sidestream smoke at home and at work was included in the analysis and an attempt was made to quantify exposure. The calculated odds ratio is not significant. There was no dose-response relationship. The original 200 cases and controls were age-matched. However, these who had never smoked could have had another age distribution and no age standardisation was carried out. This study does not support the hypothesis that passive smoking causes lung cancer.

Kabat and Wynder

The authors [25] compared 134 nonsmokers out of 2668 lung cancer patients with 134 nonsmoking controls, which were age-, race- and hospital-matched. The groups were comparable regarding religion, proportion of foreign born, marital status, residence, alcohol consumption and Quetelets index. Male cases tended to have higher proportions of professionals and to be more highly educated than controls. No difference in occupation or occupational exposure was seen in men. The histological type of lung cancer in lifelong nonsmokers and in smokers was described for 882 men and 652 women. Information on passive smoking was available in 25 male cases and controls and in 53 female cases and controls. Spouses' current or past smoking habits were known in 36 cases and controls. There was no increase in risk comparing exposure at home or at work in women, and in men at home. Only in the subgroup of men with exposure at work was there a risk increase for the cases, the difference being just significant ($P \leq 0.05$). Such subgroup analyses are however misleading. Overall this study does not support the hypothesis that passive smoking causes lung cancer.

Miller

In this paper [43] information was gathered (telephone interviews with the next of kin) from 1838 cases out of 4130 deaths in Pennsylvania during 1975 and 1976. Nonsmoking women ($n = 537$), who were married and of whom there was information on the smoking habits of the husband, were analysed.

Odds ratios were calculated for various subgroups comparing all cancer deaths with all deaths by other causes regarding the smoking habit of the husband. The author concluded that the results of the study provide support for the hypothesis that long-term passive smoking leads to excess cancer deathrates in

exposed nonsmokers. The data simply do not support such an hypothesis. In particular:

– 44% of the available deaths were omitted because of incomplete information.
– If the correct formulas are applied to the data and if age standardization is performed, the odds ratios are well within chance limits.
– Confounding factors and bias in reporting are not seriously considered.

This study, since it was not performed according to the state of the art, adds nothing to our knowledge.

Garfinkel et al.

In this case-control study [14] the authors compare 134 carefully selected nonsmoking women with lung cancer to 402 controls with cancer of the colon/rectum. The cases were selected from hospital records and special attention was given to a verified histological diagnosis. The exposure to passive smoking was assessed by a standard interview and a quantification of the exposure was attempted. The overall result was – considering the total exposure at home and at the working place – that there is no significant risk increase. The odds ratio was 1.28 for the exposure during the last five years and 1.12 for the last 25 years. There was no dose-response relationship regarding the overall exposure. Analysing various subgroups, there was one subgroup with a marginally significant risk increase: women married to men smoking more than 20 cigarettes per day at home (OR = 2.11, $P \leq 0.05$). There is no evidence of a passive smoking relationship where the data come from the woman or her husband. The odds ratios (OR) increased if the exposure history was not taken from the patient herself or from her spouse, but rather from other relatives or friends. A logistical regression analysis, adjusting for age, hospital, socio-economic status and year of diagnosis, arrived at approximately the same type I error rate.

This meagre result is weakened by the following considerations:

– A bias due to misclassification of active smoking might exist. The smoking habit was assessed in more than half of the cases not by themselves or by their husbands, but rather by their children or someone else. This was done several years after the diagnosis, in many cases several years after death, and the relevant information had to include the time 20 and more years before. Active smoking of some cases that long ago might not have been known to the person interviewed.
– There is no evidence of an association when the data on smoking habits came from the woman themselves or from their husbands; it only appeared when the daughter, son or another person supplied the information.
– A lot of odds ratios were calculated in subgroups, which were not independent. If one adjusted for multiple testing, none of the slightly significant numbers would remain significant. The analysis of subgroups using confidence intervals quite often leads to invalid results and in this study also the negative fluctuations around the chance level have to be considered.
– The study presents direct evidence that misclassification of the subject smoking habits can bias estimates of passive smoking upwards. A strong associa-

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– The high percentage of adenocarcinomas which are less typical of active smoking could explain the meagre result of this study.

The study does not provide evidence to support the hypothesis that passive smoking causes lung cancer.

Lee et al.

In the latter part of a large hospital case-control study [36] of 56 lifelong, nonsmoking lung cancer cases who were married once, 34 spouses were successfully interviewed on their cigarette consumption. A wide range of potential confounding factors was considered. The spouses of 80 matched controls, whose condition was not related to smoking, were interviewed in the same way. Various odds ratios were calculated. Passive smoking was not associated with any significant increase in risk of lung cancer amongst lifelong nonsmokers. The overall relative risk was 0.80 with an upper confidence limit of 1.50, which is less than some of the larger increases claimed in other studies. The authors discussed limitations of past studies and concluded that any risk increase by passive smoking is at most small and may not exist at all.

The number of cases in this study is small and the type II error is therefore large. The study does not contribute positive evidence to the hypothesis that passive smoking causes lung cancer, nor does it disprove it.

Akiba et al.

Lung cancer cases and controls from Hiroshima and Nagasaki atomic bomb survivors were compared in this study [1]. There were 113 nonsmoking lung cancer cases, 94 of them women. Various odds ratios were calculated. The authors reported an overall odds ratio of 1.5 for lung cancer among nonsmoking women whose husbands smoked, which was just not significant at conventional levels. The risk tended to increase with amount smoked by the husband and to decrease with cessation of exposure.

Most of the cases had died before the study was conducted. In only about 10% of the cases could the smoking habits of the husband and other information be obtained directly from the cases. Only 52% of the cases were verified by autopsy. There is some possibility of bias in this study left: a fact that led the authors to conclude that further studies were warranted where passive smoking exposure could be more fully quantified.

Dalager et al.

The authors [9] combined the cases from three case-control studies which had been published earlier [3, 7, 62]. Ninety-nine nonsmoking, histologically confirmed lung cancer cases were compared to 736 controls. The cooperation rate, the source of passive smoking data, the gender groups included, the racial

groups included and the study design varied between Louisiana, Texas and New Jersey. The original studies had opposite outcomes, Louisiana showing a positive relationship, and Texas a negative one. Only the home exposure to passive smoking was considered. There was no increase in the risk of lung cancer controlling for gender, age and study area as confounders (OR = 0.84). Searching in subgroups, several analyses were performed leading to an odds ratio of 1.47 (only Louisiana and New Jersey, only smoking pattern of spouse), which was not significant. A dose-response relationship occurred only among females with increasing pack-years of exposure to spouse smoking, with an OR = 2.99 for females with more than 35 pack-years of exposure. Here studies were not combined, and only Correa's Louisiana data were reiterated. Considering histological types, the adjusted odds ratios were also not significant. The highest OR = 2.88 was found for squamous and small cell carcinoma.

Most of the calculated odds ratios do not approach significance levels. The same sources of bias are existent here as in the study from Correa. Subgroup analyses have no confirmatory value. There was no adjustment for multiple testing. Misclassification might be present. The study does show that the same type of bias could be present in all three case control studies. Especially in older females, whose husbands are heavy smokers, bias might be more important. Any effect seen was limited to one of the three states, was of marginal significance and of doubtful validity. This study, combining data from three sources and searching in subgroups, does not contribute convincing evidence for the hypothesis that passive smoking causes lung cancer.

Knoth et al.

This study [27] is not a case-control study in the strict sense. The authors found that from 39 female nonsmoking lung cancer cases, 24 (61.5%) were married to a smoking husband or were living together with a smoker. They compared this percentage with the percentage of smoking men 50 to 69 years of age in the population, which was, according to their sources, nearly three times smaller (22.4%). They felt that passive smoking was the most likely explanation. In comparing these two percentages, other explanations are at least equally likely.

The real percentage of female nonsmoking lung cancer cases married to smoking males might be smaller than the one calculated from the study group. The smoking habit was known only for approximately 35% of the original group, making selection bias and interview bias a distinct possibility. More answers can be expected from couples with a smoking husband. The duration of smoking and the time of exposure was not clearly specified, nonsmoking men who had been smokers were also included. The percentage of female lung cancer cases married to cigarette smokers is not a valid indicator of exposure.

On the other hand, the percentage to be expected in such a group was not estimated properly. Around 38.6% of the men were active smokers in the "microcensus" conducted by the Federal Office of Statistics in 1980. In this census the definition of smoking is different from the one used in the study group. The selected age of 50 to 69 years is not well matched to the age of men in the study group and 22.4% was the average percentage of both male and

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female smokers. 58% of all men and women in Germany are smokers at some time during their life [40] and of these 36.7% are smokers. The percentage of men who smoked sometime during their life is higher than 58% in the older age groups in men, most likely around two thirds of the population. It is therefore not unexpected that 61.5% of female lung cancer cases were married to such men.

Comparing two improperly estimated percentages is not an acceptable method for epidemiological reasoning. This study adds nothing to the evidence that passive smoking might cause lung cancer.

Epidemiological evidence

To date, there have been no animal studies published in which lung cancer is produced by applying sidestream smoke. Evidence on a causal relationship between passive smoking and lung cancer can therefore only be based on epidemiological studies in man.

Of the three prospective studies, only one [18, 20] shows a moderate risk increase of 1.74. This study by Hirayama cannot be regarded as really indicative, because it might be seriously flawed. It is, however, the only study which, since it does give some empirically sound evidence, should be taken seriously.

Of the 12 case-control studies, two [27, 43] contribute nothing to the evidence, six show a moderate risk increase [1, 8, 9, 14, 50, 56], but do not sufficiently exclude chance, bias and confounding, four studies [6, 25, 29, 36] show a moderate risk decrease or no risk change. The histological type of tumor is not adequately reported in most of the case-control studies, the exposure is not assessed with reasonable validity, and interviewer bias might be present in most of them.

The major trend of the evidence in the published studies is not clearly in favour of the hypothesis. There is no single study published so far according to the state of the art of epidemiological research which gives reasonable, sound evidence.

All studies with positive associations can just as well be explained by change, bias, confounding or misclassification. Such poorly conducted and inconclusive studies cannot be added or pooled to get convincing evidence, as has been attempted in serious efforts to evaluate the situation [16]. Science should disregard poor studies. False plus false does not equal true.

Going through the eight accepted criteria mentioned in the introduction, only two of them – dose-response relationship and statistical significance – are partly fulfilled if one treats the Hirayama study as conclusive. There is no consistency in the various studies in the sense that the same results are reproduced in similar circumstances. On the contrary the results vary widely. The relative risk increase is small and at best around 2. The exposure and the effect have not been measured with validity and specificity. Bias and confounding factors have not been carefully excluded. There are no intervention studies. The biological plausibility is not convincing. Overall a causal connection cannot be inferred. Applying the IARC levels of evidence, one comes to the conclusion: in-

adequate evidence. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk [23].

Discussion

If passive smoking were an important causal factor for lung cancer, smoking pipes would be a much higher risk for lung cancer than it is. Nonsmoking barkeepers and stewards should have increased lung cancer incidence, which has not been shown. Lung cancer would be much more frequent among nonsmokers – only 5 to 10% of lung cancer cases are nonsmokers. There would also have to be an increase in the incidence of lung cancer in nonsmokers, but this incidence has been rather stable during the last decades [13, 61], as far as we know. There should be histological pre-stages in passive smokers as there are in smokers. This is also not known.

Recent studies [26, 35] have shown that misclassification alone can explain the results of the available case-control studies. Estimating the exposure to passive smoking by cotinine measurements in urine [2, 40, 41] without quality control, and in the way as it has been done in studies so far [42, 58], is not a valid and reliable indicator of exposure of individual cases. A recent evaluation of the evidence on passive smoking [46] could not consider these facts, which were presented at a symposium [45] in October 1986. Whether the presence of many animal carcinogens in sidestream smoke alone – contrasted by missing epidemiological evidence – is a reasonable argument for the assumption that passive smoking causes lung cancer in man, remains an open question.

The toxicological evidence as summarized in [16] is based on exposure data and one the existence of carcinogenic and mutagenic substances in sidestream smoke alone. It is well known that the yield (per cigarette) of several carcinogenic substances and tar is higher in sidestream smoke than in mainstream smoke. The differences are partly due to modern filter techniques. However, analytical measurements of carcinogenic substances in sidestream smoke vary 2 to 10 times, depending on the measuring techniques. The dilution in the air and the physical and chemical processes in the air one or more hours after pollution by sidestream smoke have only recently been investigated [53], showing a fast decay of toxic effects within a short time. To what extent the various carcinogenic substances in sidestream smoke dilute or decay, depending for instance on time length, should be further investigated. Whereas the absorption of nicotine and its pharmacokinetic and metabolism are relatively well known, this does not hold for a single carcinogenic substance contained in sidestream smoke. The amount of absorption of these substances – not the amount inhaled –, how they act on the lung tissue, the metabolic pathways in the body and the way in which they act in man, are not known.

What is known is that there are many carcinogenic substances in sidestream smoke in very small concentrations. The evaluation of this fact depends on the frame of reference. If there is really no threshold for carcinogenic substances – which is the paradigm to which some leading toxicologists presently adhere, but

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which might not be valid for a variety of reasons – and if every risk increase, however small and unlikely it could be, should be avoided, the conclusion must be that passive smoking should be banned from toxicological evidence alone. The first "if" will be answered by toxicology during the next decade and the second "if" should be left to decisions of the society and its institutions and not to toxicologists alone.

We should do all we can to reduce active smoking. Using the argument that epidemiological studies show passive smoking causes lung cancer – if this is not true – might be an obstacle to this goal in the long run. Such a possibly wrong argument might have serious negative effects on the credibility of epidemiology, which should be neither servant of the spirit of the age nor maid of toxicology. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

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The risk ratios for passive smoking can be surprisingly high (up to 2 or 3), as reported both by Correa et al and others.[8,9] These risk ratios would be more consistent with those found for active smoking, particularly among women, if the active smoker is at greater risk also from his or her own passive smoke, again through the absorption of radioactivity on the smoke particles passively inhaled; also the relatively higher toxicity of the sidestream smoke[10] might be important.[11] These and other aspects (eg, the urban-rural difference in lung cancer risk from smoking) are more thoroughly discussed elsewhere[12] in the context of indoor radon daughters. Finally, in view of the long latency periods observed among miners acquiring lung cancer from radon daughter exposure,[13] one might suggest that the children of smoking mothers obtain an early exposure to increased levels of radon daughters at home and that smoking later in life promotes the development of lung cancer.

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HANS BERGMAN
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LUNG CANCER AND PASSIVE SMOKING

SIR,—I was surprised to read, in Professor Trichopoulos and colleagues' letter (Sept 17, p 677), a German study of passive smoking and lung cancer described as having yielded "positive" results. The paper cited[1] contains only tentative conclusions based on poor data analysed by unacceptable methods.

I was also surprised that the findings from the Greek hospital study of passive smoking and lung cancer were almost identical to those reported two years ago[2] despite a substantial increase in the numbers of cases and controls. In the 1981 report the relative risks of lung cancer for non-smoking women were 1, 1·8, 2·4, and 3·4 according to whether their husbands did not smoke, were ex-smokers, or were current smokers of 1–20 or 21 or more cigarettes a day; the updated relative risks are 1, 1·9, 2·4, and 3·4, respectively.

In the 1981 paper the relative risks agreed exactly with the appropriate cross-product ratios calculated from the numbers of cases and controls in the relevant category for husbands' smoking. In the latest results, despite the method being apparently identical, there is a clear disagreement between the relative risks provided by Trichopoulos et al and those I calculate (see table).

RELATIVE RISK OF LUNG CANCER ACCORDING TO SMOKING HABITS OF HUSBAND

Group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)	
			1–20	21+
RR (quoted)	1·0	1·9	2·4	3·4
RR (calculated)	1·0	1·9	1·9	2·5

Relative risk = ratio of risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers.

My calculations suggest that the latest data do not show as clear an association between a woman's lung cancer risk with her husband's smoking habits as the earlier data did. Indeed, relative risks calculated from the additional data are 1, 2·0, 1·8, and 1·8 and do not show the dose-response relation seen earlier. This doubt, added to doubts about the histological evidence and the use of cases and controls from different hospitals (limitations which Trichopoulos et al concede), prompts one to ask if the study really does add to the evidence implicating passive smoking as a factor in lung cancer.

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POTASSIUM CHLORIDE SUPPLEMENTS

SIR,—As your Round the World correspondent predicted,[1] the US Food and Drug Administration advisory committee meeting of March 2 on the controversy of wax-matrix versus microencapsulated potassium chloride preparations proved inconclusive. A few points about this controversy are worth noting.

The study by McMahon et al,[2] showing a favourable result for 'Micro-K' (A. H. Robins) in comparison with 'Slow-K' (Ciba-Geigy) was sponsored by Robins. The study by Patterson et al,[3] showing no difference between micro-K and slow-K, was sponsored by Ciba-Geigy. Both studies have been confirmed by other studies sponsored by the respective company.

Ciba-Geigy, while denying that slow-K is more ulcerogenic than micro-K, has bought from Alfred Benzon Ltd, Denmark, a licence for 'Kalinorm', a microencapsulated (pellet) preparation of KCl similar (or identical) to micro-K. It seems remarkable that Ciba-Geigy is planning to market this preparation when, according to Ciba-Geigy's US subsidiary, "Slow-K has an established clinical record unparalleled by any other solid K supplement".

It seems that, privately, Ciba-Geigy has concluded that kalinorm is as good as micro-K, and that it is better than slow-K, but they would presumably consider it scientifically incorrect to conclude that micro-K is better than slow-K.

Finally I would emphasise, as your RTW correspondent did, that doctors should "re-evaluate the decisive need for a potassium supplement and, if the indication is clear, prescribe it as a liquid". The findings of Patterson et al[3] clearly support this.

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**This letter has been shown to Dr Burley, whose reply follows.—ED. L.

SIR,—One of the main reasons why slow-release formulations of potassium were developed was the unacceptability of liquid potassium. Indeed, Patterson et al[3] reported that KCP elixir was poorly tolerated in their trial, giving rise to abdominal pain and heartburn in 9 of the 15 volunteers (60%). Dr Hansson omits to mention this. The issue is therefore whether the risk/benefit ratio of 'Slow K' is acceptable. There are eighteen years of clinical experience with slow K in the UK, during which over 4·5 million patient-years of treatment has been prescribed: with 'Micro K' formulations there is almost no clinical experience. Less than 50 cases of significant alimentary side-effects have been reported with slow K, and some of these were manifestly brought about by previous strictures or oesophageal obstruction due to cardiac enlargement. It would be hard to point to a comparable safety record with any other widely used drug. The fact that a company may be investigating or pursuing alternatives is an indication of interest and involvement in the area, and should not be interpreted as a loss of confidence in an existing product.

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DENIS BURLEY

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RISK ESTIMATES FOR NONSMOKER LUNG CANCER
BASED UPON MODELING PROCEDURES

- In 1985, Repace and Lowrey published an article claiming that exposure to ETS is responsible for 500 to 5,000 lung cancer deaths per year in the United States.[1] This report received extensive press coverage upon its release.

- The report contains two highly theoretical models for estimating risks of lung cancer from ETS exposure. One model relies upon a "reinterpretation" of the epidemiologic studies of lung cancer in nonsmokers; the second model estimates lung cancer mortality among nonsmokers based on a single study dealing with the Seventh Day Adventists, a religious group known for its vigorous opposition to smoking.

- Critics of the Repace and Lowrey approach have pointed out that the estimates are based on errors and "unrealistic assumptions" which result in overestimations of exposure.[2] One analysis of the model showed that, depending on the assumptions and input data used, the estimates are inherently inaccurate and may vary by as much as 300-fold.[3] Another scientist noted that the exposure and dose levels used in the modeling exercise were not based on actual measurements; such measurements reported elsewhere range from "ten- to one-hundred-fold less than that in the Repace and Lowrey model."[4]

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- Other criticisms have focused on the report's methods of analysis,[5-7] and suggest that Repace and Lowrey failed to control for other confounding factors, and that their model did not provide "the very statistical bases of estimation procedures."[4]

- Repace and Lowrey's estimate of nonsmoker lung cancer risks in the workplace was also criticized by scientists who noted that <u>none</u> of the epidemiologic studies of ETS exposure and disease in nonsmoking working women report a statistically significant increase in risk.[2]

- Two British researchers, Darby and Pike, published a paper in 1988 describing another type of mathematical model which predicted potential effects from ETS exposure based on data from a study on active smoking.[8] Even when adjustments were made for childhood exposure to ETS, the authors reported that the model predicted a risk for nonsmokers that was smaller than "the underlying background risk for lung cancer." They concluded that their model could not explain the difference between risks reported for nonsmokers in epidemiologic studies and the low levels of ETS exposure reported in other studies.

- The Darby and Pike model was criticized in 1990 by Wald, et al., authors of one of the earlier meta-analyses on the epidemiologic studies of ETS exposure and lung cancer incidence.[9] Wald's group questioned Darby and Pike's conclusion that there was a discrepancy between risks estimated by epidemiologic studies and by exposure data. Darby and Pike replied that the existing cotinine data employed by Wald, et al., were possibly both insufficient and inappropriate to allow an adequate comparison to be made with the epidemiologic data.[10]

- In 1991, Peter N. Lee published an article investigating the process of risk assessment as applied to the spousal smoking data.[11] After reviewing a number of potential sources of bias in the epidemiological literature, as well as commenting on the conclusions of the authors of previous risk assessments, Lee concludes:

> The epidemiology has indicated a magnitude of risk in relation to spouse smoking that is implausibly large compared with what is known about the extent of ETS exposure involved. There are clear weaknesses and sources of bias in the epidemiology which could invalidate risk assessments based on it. The most important of these are misclassification bias and failure properly to compare like with like in case-control studies, but failure to properly take confounding variables into account and publication bias are also relevant.

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Lee continues:

> All three risk assessments criticised in this document take the epidemiology virtually at face value, with no real discussion at all of its weaknesses. Thus Kawachu et al mentions only publication bias (and dismisses it), while Wells considers only misclassification bias (and then inadequately corrects for it). Repace and Lowrey do not discuss any sources of bias at all . . . No reasonable scientific criteria are used to decide what constitutes a valid study before it can be included in a risk assessment -- studies conducted with complete disregard of basic scientific principles are included as if they were as valid as carefully designed studies.

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11. Lee, P.N., "Weaknesses in Recent Risk Assessments of Environmental Tobacco Smoke," Environmental Toxicology 12: 193-208, 1991.

Lee continues:

> All three risk assessments criticised in this document take the epidemiology virtually at face value, with no real discussion at all of its weaknesses. Thus Kawachi et al mentions only publication bias (and dismisses it), while Wells considers only misclassification bias (and then inadequately corrects for it). Repace and Lowrey do not discuss any sources of bias at all . . . No reasonable scientific criteria are used to decide what constitutes a valid study before it can be included in a risk assessment -- studies conducted with complete disregard of basic scientific principles are included as if they were as valid as carefully designed studies.

- Finally, while not truly a risk assessment, a review article published in 1993 by Michael Siegel purported to present data supporting the position that ETS exposure posed a lung cancer risk to persons employed in restaurants and bars.[12] Siegel's paper was based on two premises: that ETS exposures were higher in restaurants and bars than in other indoor environments, and that food-service workers had a higher risk of lung cancer than the general population. Siegel compared these two disparate sources of data to reach his conclusion that a 50% increase in lung cancer risk among food-service workers could be attributable to ETS exposure in the workplace.

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A QUANTITATIVE ESTIMATE OF NONSMOKERS' LUNG CANCER RISK FROM PASSIVE SMOKING

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This work presents a quantitative assessment of nonsmokers' risk of lung cancer from passive smoking. The estimates given should be viewed as preliminary and subject to change as improved research becomes available. It is estimated that U.S. nonsmokers are exposed to from 0 to 14 mg of tobacco tar per day, and that the typical nonsmoker is exposed to 1.4 mg per day. A phenomenological exposure-response relationship is derived, yielding 5 lung cancer deaths per year per 100,000 persons exposed, per mg daily tar exposure. This relationship yields lung cancer mortality rates and mortality ratios for a U.S. cohort which are consistent to within 5% with the results of both of the large prospective epidemiological studies of passive smoking and lung cancer in the United States and Japan. Aggregate exposure to ambient tobacco smoke is estimated to produce about 5000 lung cancer deaths per year in U.S. nonsmokers aged ≥ 35 yr, with an average loss of life expectancy of 17 ± 9 yr per fatality. The estimated risk to the most-exposed passive smokers appears to be comparable to that from pipe and cigar smoking. Mortality from passive smoking is estimated to be about two orders of magnitude higher than that estimated for carcinogens currently regulated as hazardous air pollutants under the federal Clean Air Act.

Introduction

Exposure of nonsmokers to indoor air pollution from tobacco smoke (also known as involuntary or passive smoking) has recently become a public health concern (USSG, 1982) for several reasons: such exposure is widespread (Repace and Lowrey, 1980; Friedman *et al.*, 1983); studies of the effects of tobacco smoke on smokers worldwide have implicated it as the most important cause of lung cancer (USSG, 1982; Doll and Peto, 1981); existence of a threshold for carcinogenesis is doubtful (USSG 1982; IRLG, 1979; U.S. EPA, 1979a; IARC, 1979; Pitot, 1981); and there is suggestive new evidence of lung cancer (and other serious health effects) in nonsmokers exposed to ambient concentrations of tobacco smoke (Trichopoulos, 1981, 1983; Hirayama, 1981a, 1981b, 1983a, 1983b; Garfinkel, 1981; Correa *et al.*, 1983; Knoth *et al.*, 1983; Gillis *et al.*, 1983; Koo *et al.*, 1983; Kabat and Wynder, 1984; Miller, 1984; Sandler *et al.*, in press a,b).

There are three important fractions of tobacco smoke: mainstream smoke, which the smoker inhales directly into the lung; exhaled mainstream smoke, that fraction of the mainstream smoke which is not retained in the lungs of the smoker, and sidestream smoke, that fraction of tobacco smoke emanating directly from the burning end of the cigarette into the air. Nonsmokers are commonly exposed to tobacco combustion products in diluted sidestream and exhaled mainstream tobacco smoke from cigarettes, cigars, and pipes (Repace and Lowrey, 1980). Tobacco smoke contains 60 known or suspect carcinogens, including 51 in the phase containing particulate matter; the carcinogenic activity of tobacco smoke appears to require this phase (USSG, 1982). Animal bioassays indicate that sidestream tobacco tar is more carcinogenic per unit weight than mainstream tar (Wynder and Hoffman, 1967). For public health purposes, it will be assumed that mainstream and sidestream smoke have similar human carcinogenic potency.

In his 1982 report on cancer and smoking (USSG, 1982), the U.S. Surgeon General asserted that despite the incompleteness of the evidence, nonsmokers should

*The views presented in this article are those of the authors, and do not necessarily reflect the policies of their respective agencies.

avoid exposure to second-hand smoke to the extent possible, a risk-management judgement supported by the World Health Organization and the National Academy of Sciences (WHO, 1979; NRC, 1981).

This raises the question of whether the quantity of tobacco tar to which the average nonsmoker is exposed creates a significant risk of lung cancer. In order to answer this question, a quantitative risk assessment is first justified and then performed. Risk assessment is the use of science to define the health effects of exposure of individuals or populations to hazardous materials or situations (NRC, 1983). Risk assessments contain some or all of the following four steps:

(1) Hazard identification – the determination of whether a particular chemical is or is not causally linked to certain health effects.

(2) Dose-response assessment – the determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.

(3) Exposure assessment – the determination of the extent of human exposure before or after application of regulatory controls.

(4) Risk characterization – the description of the nature and often the magnitude of the human risk, including attendant uncertainty.

In other words, quantitative risk assessment deals with the question of how much morbidity and mortality an agent is likely to produce given specified levels of exposure. Typically utilized in the regulation of carcinogens, it is important because control efforts cannot proceed without assurance that the health gains are worth the cost (Lave, 1983; Albert, 1983). On the basis of such assessments, informed risk management judgements can be made.

This work draws upon the epidemiology of lung cancer (USSG, 1982; Pitot, 1981; USSG, 1979; Ives, 1983) and on indoor air pollution physics (Repace and Lowrey, 1980, 1982; NRC, 1981) to produce a risk analysis (IRLG, 1979; U.S. EPA, 1979a; Lave, 1983; COST, 1983; Fischoff *et al.*, 1981; NRC, 1983) in which nonsmokers' lifestyles are correlated to exposure to airborne tobacco tar, and incidence of lung cancer. This analysis first reviews estimates of the average exposure of the general population of ambient tobacco smoke. Second, it reviews studies linking tobacco-related disease in nonsmokers to exposure-related variations in lifestyle. Third, it couples these two factors to develop a phenomenological estimate for the aggregate lung cancer risk to the U.S. nonsmoking population, and develops an exposure-response relationship for the estimation of the risk to the most-exposed. Fourth, it compares the estimated level of lung cancer mortality and resultant loss of life expectancy from passive smoking to those from cigarette, pipe, and cigar smoking. Fifth, it compares the predictions of alternate exposure-response relationships with the results of two large prospective epidemiologic studies of passive smoking and lung cancer, and performs a sensitivity analysis. Finally this work compares the estimated risk from ambient tobacco smoke to that from various airborne carcinogens currently being regulated in the United States as hazardous air pollutants, to place the significance of the estimated risk in perspective.

Variation of Exposure with Lifestyle

In earlier work (Repace and Lowrey, 1980, 1982, 1983, 1984; Repace, 1981, 1982, 1983, 1984, in press; Repace *et al.*, 1980, 1984; Bock *et al.*, 1982) factors affecting nonsmokers' exposures to tobacco smoke were studied, and field surveys of the levels of respirable particles were conducted indoors and out, in both smoke-free and smoky environments. This work established that ambient tobacco smoke imposed significant air pollution burdens on nonsmokers, and, using controlled experiments (Repace and Lowrey, 1980, 1982, 1983), a model was developed to estimate those exposures. This model predicts that the exposure of U.S. nonsmokers ranges from 0 to 14 mg of cigarette tar per day (mg/d), depending upon the nonsmokers's lifestyle. As derived in Appendix A and shown in Table 1, the average population exposure for adults of working age, averaging over the work and home microenvironments, is about 1.43 mg/day (Repace and Lowrey, 1983) with an 86% exposure probability.

Table 1, derived from the model in Appendix A, estimates probability-weighted exposure to the particulate phase of ambient tobacco smoke for a typical U.S. adult nonsmoker. Exposures received in other (Repace *et al.*, 1980) indoor microenvironments, outdoors, and in transit, which account for the remaining 12% of people's time, were omitted. Table 1 is derived from considerations that ambient concentrations of tobacco tar have been found to be directly proportional to the smoker density and inversely proportional to the ventilation rate (Repace and Lowrey, 1980). Ventilation rate tables given by ASHRAE (1981), can be used to estimate both the range in ventilation rate (from the design mechanical rates) and smoker density (from the design occupancies), and thus upper and lower bounds and average concentrations for model workplace and home microenvironments can be estimated.

Table 1 suggests that individuals receiving exposure both at home and at work constitute a high exposure group, with the workplace appearing four times as strong a source of exposure as the home; the reason for this differential is the generally higher occupancy (i.e., smoker density) encountered in the workplace (Repace and Lowrey, 1982; ASHRAE, 1981). This estimate of exposures represents a modeled weighted average taken over the entire population, including those who are not exposed.

Table 1. Estimated probabilities of nonsmokers' exposure to tobacco smoke at home and at work (after Repace and Lowrey, 1983; Appendix A):* Nonexclusive probability of being exposed at work: 63%; probability of *not* being exposed at work: 37%. Nonexclusive probability of being exposed at home: 62%; probability of *not* being exposed at home: 38%.

Lifestyle: Daily Average Probability of Being Exposed (Rounded Values)		Exposure (mg) Modeled Daily Average	Exposure (mg) Daily Probability-Weighted
At work and at home: %	63 x 62 = 39	2.27	0.89
Neither at work nor at home: %	37 x 38 = 14	0.00	0.00
At home but not at work: %	62 x 37 = 23	0.45	0.10
At work but not at home: %	63 x 38 = 24	1.82	0.44
Total: %	100		1.43

*The estimated exposure to the particulate phase of ambient tobacco smoke for U.S. adults of working age, at work and at home (these two microenvironments account for an estimated 88% of the average person's—both smokers and nonsmokers—time), determined from average concentrations of tobacco smoke calculated for model workplace and home microenvironments, weighted for average occupancy, as derived in Appendix A.

Jarvis and Russell (in press), in a study of urinary cotinine (a nicotine metabolite) in a sample of 121 self-reported nonsmokers, state that only 12% of subjects had undetectable cotinine levels, despite nearly 50% reporting no passive smoke exposure. In a study of 472 nonsmokers, Matsukura (1984) examined the relationship of urinary cotinine to the smokiness of their environment, and found that nonsmokers who lived or worked with smokers had higher cotinine levels than those who did not. Matsukura *et al.*, (1984) also found that cotinine levels increased with the number of smokers present in the home and the workplace; however, none of the differences were statistically significant, except for the lowest urinary cotinine level of the nonsmokers who were not exposed to tobacco smoke in the home or the workplace. These studies respectively illustrate the widespread exposure of nonsmokers to ambient tobacco smoke, and the relative importance of the domestic and workplace microenvironments in such exposures.

Epidemiological Evidence for the Variation of Risk with Lifestyle: Pulmonary Effects

White and Froeb (1980) evaluated the effect of various degrees of long-term (>20 yr) workplace exposure to tobacco smoke on 2100 healthy middle-aged workers. Of these workers, 83% held professional, managerial, or technical positions, while the remaining 17% were blue-collar workers. Relative to those not exposed at home or at work, passive smokers of both sexes suffered statistically significant declines in mid- and end-expiratory flow rates which averaged about 13.5% and 22% respectively, and did not differ significantly from the values measured in noninhaling or light smokers of cigarettes, pipes, and cigars. They concluded that chronic exposure to tobacco smoke in the work environment reduces small airways function to the same extent as smoking 1 to 10 cigarettes per day.

Kauffmann *et al.* (1983) compared pulmonary function in about 3800 people in France: 849 male "true" nonsmokers (defined as those not exposed at home), 165 male passive smokers (defined as those exposed at home), 826 female "true" nonsmokers, and 1941 female passive smokers. The authors restricted the analysis to subjects aged 40 yr or older (i.e., to those who had been exposed for 15 or more years to smoking by their spouses) and who were living in households with no persons over the age of 18 yr except their spouses. They found that nonsmoking subjects of either sex whose spouses were current smokers of at least 10 g (about 10 cigarettes) of tobacco a day had mid-expiratory flow rates averaging 11.5% lower than those married to nonsmokers. For women in social classes with the highest percentage of paid work, the effect of workplace smoking appeared to confound the effect of passive smoking at home. However, in the large subgroup of women without paid work (i.e., not exposed to workplace smoking), a clear dose-response relationship to amount of husbands' smoking was observed. They concluded that women living with heavy smokers appeared to have the same reductions in mid-expiratory flow rates as light smokers, and that after 15 yr exposure in the home environment, passive smoking reduces pulmonary function.

A third study by Kasuga (1983) of urinary hydroxyproline-to-creatinine (HOP-r) ratios as a function of passive smoking status showed that HOP-r levels in nonsmoking wives and children varied in a dose-response relationship with husbands' and parental smoking habits, when adjusted for pre-existing respiratory disease. Kasuga (1983) asserts that HOP-r serves as a marker to detect deleterious active and passive smoking effects on the lung, before and after the manifestation of clinical symptoms, and that urinary HOP-r in light-smoking women is almost equivalent to HOP-r in nonsmoking wives with heavy-smoking husbands.

These three epidemiologic studies provide evidence that variations in the exposure of adult nonsmokers to ambient tobacco smoke at home and, particularly, at

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work, can produce observable pulmonary effects. Like effects have been observed in children exposed at home (Tager *et al.*, 1983).

Cancer

Thirteen epidemiologic studies have explicitly examined the lung cancer risk incurred by the nonsmoking spouses of cigarette smokers. In all but one study, the only exposure variable was the strength of the spouse's smoking habit. The studies were conducted in Greece (Trichopoulos *et al.*, 1981, 1983), Japan (Hirayama, 1981a, 1981b, 1983a, 1983b), the United States (Garfinkel, 1981; Correa, *et al.*, 1983; Kabat and Wynder, 1984; Miller, 1984; Sandler, *et al.*, a and b, in press), Germany (Knoth *et al.*, 1983), Scotland (Gillis *et al.*, 1983), and Hong Kong (Chan and Fung, 1982; Koo *et al.*, 1983).

In the Greek study, Trichopoulos *et al.* (1981, 1983) used the case-control technique: involuntary exposure to cigarette smoke as measured by the husbands' daily consumption was found to increase the average risk of lung cancer by a factor of 2.4 ($p < 0.01$) when 77 lung cancer patients were compared to 225 controls, and a dose-response relationship was observed. Divorce, remarriage, husband's death, and change in smoking habits were considered.

In the Japanese study (from 1966 to 1981) of lung cancer in 91,540 nonsmoking women, Hirayama (1981a, 1981b, 1983a, 1983b) used the prospective technique: relative to those women not exposed at home (controls), involuntary exposure of wives of smokers was found to increase the average risk of lung cancer by a factor of 1.78 ($p < 0.001$), where the exposure was also estimated from husbands' daily consumption. The annual lung cancer death (LCD) rate in the controls was 8.7 per 100,000. Hirayama found that the exposed wives experienced an average annual increase in lung cancer mortality rate of 6.8 per 100,000, with a range of 5.3 to 9.4 per 100,000, in a dose-response relationship depending upon the degree of the husband's smoking. Hirayama found further that the risk of lung cancer death in nonsmoking women increased both with the time of exposure and number of cigarettes smoked daily by the husband. Hirayama also reported a factor of 2.9 (± 0.3, at the 95% confidence level) for increased risk of lung cancer in 1010 nonsmoking husbands with smoking wives.

More recently, Hirayama extended his earlier work to suggest increased risk of nasal sinus cancer, and ischemic heart disease in passive smokers, and evidence of decreased lung cancer risk in nonsmoking wives of exsmokers. With respect to cancer of the para-nasal sinuses in nonsmoking wives ($n = 28$), Hirayama found standardized mortality ratios of 1.00, 2.27, 2.56, and 3.44 when husbands were nonsmokers, smokers of 1-14, 15-19, and >20 cigarettes per day, respectively ($p = 0.01$). For ischemic heart disease, risk elevations for nonsmoking wives ($n = 494$) with the extent of husbands' smoking were reported, with standardized mortality ratios of 1.00, 1.10, and 1.31 when husbands were nonsmokers, smokers of 1-19, and >20 cigarettes/day, respectively ($p < 0.02$). For lung cancer, the standardized mortality ratio of lung cancer in nonsmoking women ($n = 200$) was 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, exsmokers, daily smokers of 1-14, 15-19, and >20 cigarettes/day, respectively.

In the first U.S. study, Garfinkel (1981) reported results from an analysis of data collected from the American Cancer Society's (ACS) prospective study of lung cancer risk in 176,739 nonsmoking white women (1960 to 1972) as a function of involuntary exposure as indicated by their husbands' cigarette consumption. Of the total, 72% of the nonsmoking women were married to smokers. Three smoking categories were identified: none, less than one pack (20 cigarettes) per day, or greater than one pack per day. Garfinkel reported statistically insignificant risk ratios of 1.00, 1.27, and 1.10, respectively, for the three categories (average 1.20 over the exposed categories). Also reported were age-standardized death rates, which were respectively 13.8, 12.9, and 13.1 lung cancer deaths per 100,000 person-yr for this cohort in 1960–1964, 1964–1968, and 1968–1972 (average 13.3 per 100,000 person-yr for the period 1960–1972). The death rates were standardized to the distribution of white men and women combined for the U.S. population in 1965, which decreased the rates for females "slightly."

More recently, Correa *et al.* (1983) studied 8 male and 22 female nonsmoking lung cancer cases and 180 male and 133 female controls as part of a larger study including smokers, with 1338 lung cancer cases and 1393 controls, in Louisiana. They reported that nonsmokers married to heavy smokers had an increased risk of lung cancer, as did smokers whose mothers smoked. Men with smoking wives had a nonsignificant risk ratio of 2.0 compared to their counterparts with nonsmoking wives, and women with smoking husbands had an average risk ratio of 2.07 ($p < 0.05$) compared to women with nonsmoking husbands. An exposure-response relationship was observed, with the peak risk reaching 3.5 ($p < 0.05$). The combined data for men and women passive smokers was significant ($p < 0.05$) for the heavier smoking category (≥ 41 pack-years).

A third U.S. case-control study, by Kabat and Wynder (1984), reported on passive smoking and lung cancer in nonsmokers for 25 male cases and 25 controls, and 53 female cases and 53 controls, where the majority of the patients were from New York City. The controls consisted of patients hospitalized for non-smoking-related diseases, roughly two-thirds being cancer patients. No differences on exposure to passive smoking at home or at work were found in the women. However,

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the male passive smokers displayed a statistically significant ($p = 0.05$) difference in lung cancer (odds ratio 1.6) relative to the non-exposed group.

A fourth U.S. study by Miller (1984) of mortality from all forms of cancer in 123 nonsmoking women (only 5 lung cancer cases) as a function of husband's smoking history reported a nonsignificant odds ratio of 1.4 for all women ($p = 0.15$) for women whose husbands smoked relative to those who did not; when employed women were excluded, the odds ratio increased to 1.94 and was statistically significant ($p < 0.02$).

A fifth U.S. study of Sandler *et al.* (in press a) also examined mortality from all forms of cancer related to passive smoking, in both nonsmokers and smokers [231 cases and 235 controls (70% white and 67% female); only 2 cases of lung cancer in nonsmokers] as a function of spouses' smoking habits. Cancer risk—adjusted odds ratio—(lung, breast, cervix, and endocrine) among individuals ever married to smokers was 2.0 times that among those never married to smokers ($p < 0.01$). This increased risk was not explained by confounding individual smoking habits, demographic characteristics, or social class.

In a sixth U.S. study, Sandler *et al.* (in press b) examined cancer risk in adulthood in 197 cases and 223 controls, 66% female, from early life exposure to parents' smoking. They found that mothers' and fathers' smoking were both associated with risk for hematopoietic cancers (Hodgkin's disease, lymphomas, and leukemias), and a dose-response relationship was seen for the latter two. The odds ratio for hematopoietic cancers increased from 1.7 when one parent smoked, to 4.6 when both smoked ($p < 0.001$).

In the first of two studies from Hong Kong, Chan and Fung (1982) found a lower incidence of passive smoking among 34 female lung cancer cases (40.5%) than among 66 female controls (47.5%). All patients and controls were interviewed concerning their smoking habits and those of their spouses, their cooking habits, including types of cooking fuel used. Histological diagnoses of tumors were obtained. Controls were taken from orthopedic patients.

In the second Hong Kong study, Koo *et al.* (1983) studied passive smoking in 56 female lung cancer cases and 85 female controls. Passive smoking cases had an excess of 3.8 yr of passive smoking (workplace plus domestic exposures) compared with controls, but the differences were not statistically significant ($p \leq 0.069$). However, among a subgroup of 8 marine dwellers, cases had 11.8 years more exposure than controls ($p = 0.0003$).

Knoth *et al.* (1983) reported on a study of 39 nonsmoking German females with lung cancer. 61.5% were found to have smoking spouses. The authors state that this percentage was threefold that expected on the basis of smoking habits of German males.

Gillis *et al.* (1984) reported preliminary results of a study of passive smoking and lung cancer in 91 male controls ($n = 2$) [the numbers in parentheses give the numbers of cases] without domestic passive smoking and in 90 subjects exposed at home ($n = 4$), and in 40 female controls ($n = 2$) and 58 subjects ($n = 6$). No effects of lung cancer were noted in the females, but elevated rates of myocardial infarction were reported (risk ratio 3.0). In the males, elevated rates of both lung cancer (risk ratio 3.25) and myocardial infarction (risk ratio 1.45) were reported. Gillis *et al.* state that since insufficient time has elapsed since the beginning of this study, no firm conclusions can be drawn relating to the incidence of cancer or other diseases.

Thus there are now a large number of studies providing evidence for increased risk of lung cancer from increased exposure to passive smoking. It might be expected that subgroups of the population which proscribe smoking among their membership would have a lower probability of passive smoking, and therefore should also have a lower incidence of smoking-related disease than the general nonsmoking population.

One such subgroup is the Church of Jesus Christ of the Latter Day Saints, popularly known as the Mormon Church, which advises against the use of tobacco. Enstrom (1978) found that active Mormons who were nonsmokers had standardized mortality rates for lung cancer which were 21% of those in the general population which includes smokers. This rate was found comparable to the rate of 19% for a sample of the U.S. general population "who had never smoked cigarettes." Interestingly, however, this result occurred despite the fact that 31% of the active Mormon cohort were former smokers. This confounding factor was not present for certain subgroups in the following study.

Phillips *et al.* (1980a, 1980b) have studied mortality (from 1960 to 1976) in Seventh Day Adventists (SDAs), a religious group that also follows rigorous proscriptions against the use of tobacco. As with the Mormons, SDAs have rates of mortality from lung cancer and other smoking related cancers that are fractions, 21% and 66%, respectively, of the rates for a demographically comparable group in the general U.S. population (including smokers) (1980a). Many SDAs work for church-run businesses. Thus, SDAs appear to be less likely than the general population to be involuntarily exposed to tobacco smoke, as children or as adults, at home or in the workplace, because neither SDA homes nor SDA businesses are likely to be places where smoking is permitted, and because the great majority of SDA family and social contacts are among other SDAs who do not smoke (See Appendix C).

Phillips *et al.* (1980a, 1980b) compared mortality in two demographically similar groups of Southern Californians: SDAs (from 1960 to 1976) and non-SDAs (from 1960 to 1971). A sizable subgroup (35%) of SDAs report prior cigarette use, especially among men (1980b). However, for two select subgroups of each group, 25,264 SDAs and 50,216 non-SDAs who were self-reported

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Table 2. Age-adjusted SDA-to-non-SDA ratio of lung cancer mortality (after Phillips *et al.* (1980b).*

		By Health Habit Index		
	Average	Best Third	Average Third	Worst Third
I. All SDAs	0.54	0.54	0.40	0.96
II. SDAs who never smoked	0.41	0.41	0.32	0.78

Values shown are adjusted by Mantel-Haenzel procedure ($p \leq 0.01$).

*Lung cancer mortality ratios taken from a prospective study of two demographically similar cohorts. The non-SDA come from the general south California population, and were self-reported nonsmokers who never smoked. The SDA come from a southern California subgroup less likely to engage in passive smoking by virtue of lifestyle differences. The health habit index is a measure of how faithfully individuals adhered to the Church's teachings; the worst third were also more likely to have a non-SDA spouse. (Values quoted in text are the reciprocals of numbers given here.) Phillips *et al.* (1980a, 1980b) reported results for all SDA, and reported replicating these data for SDA who never smoked, as shown. The SDA subjects and non-SDA subjects for this study consisted of white California respondents to the same four-page self-administered questionnaire collected by the American Cancer Society study of 1 million subjects throughout the United States (NCI, 1966; Garfinkel, 1981; Phillips *et al.*, 1980a, 1980b).

nonsmokers who had never smoked, age-adjusted mortality rates were compared for smoking-related and nonsmoking-related diseases. Table 2 compares age-adjusted lung cancer mortality ratios for two SDA cohorts relative to nonsmokers in the general population who never smoked. The first cohort consists of all SDA, and includes those who never smoked, exsmokers, and smokers. The first row of Table 2 gives the mortality ratios relative to the never-smoked non-SDAs in the general population. The second row compares the second SDA cohort (those who never smoked) to the non-SDA who never smoked. The values given are averaged over both sexes. From Table 2 the results show that the non-SDA group of nonsmokers who had never smoked (but who were more likely to suffer involuntary exposure to tobacco smoke) had an average lung cancer mortality rate of 2.4 times that of the never-smoked SDAs (the group less likely to have suffered such exposure by virtue of their lifestyle). This concludes the review of evidence relating variations of lifestyle to variations in lung cancer risk in nonsmokers.

Does Ambient Tobacco Smoke Pose a Carcinogenic Hazard?

The International Agency For Research on Cancer (IARC) criteria for causality to be inferred between exposure and human cancer state that confidence in causality increases when (1) independent studies agree; (2) associations are strong; (3) dose-response relationships exist, and (4) reduction in exposure is followed by reduction in cancer incidence (IARC, 1979). These criteria are applied here as follows:

1. There are now 14 studies, covering 6 cultures, indicating a relationship between exposure to ambient tobacco smoke and incidence of lung cancer. If the studies are divided into substudies of men and women, this yields 20 substudies, all but 2 of which suggested an increased cancer mortality from passive smoking, and 12 of which attained statistical significance. Moreover, the mortality ratios based on spouses' smoking as an exposure variable, cluster around the value 2.0. Thus, many independent studies agree.

2. Mainstream tobacco smoke is strongly associated with lung cancer. The U.S. Surgeon General (USSG, 1982) asserts that mainstream cigarette smoke is a major cause of cancers of the lung, larynx, oral cavity, and esophagus, and is a contributory factor for the development of cancers of the bladder, pancreas, and kidney, where the term contributory factor does not exclude the possibility of causality. Both smokers and nonsmokers are exposed to exhaled mainstream and sidestream tobacco smoke. Sidestream smoke by animal bioassay has been found to be of greater potency than mainstream smoke.

3. Five of the 14 studies reported dose-reponse relationships between passive smoking and lung cancer. Dose-response relationships between lung cancer and active cigarette smoking show increasing mortality with increasing dosage of smoke exposure, and an inverse relationship to age of initiation (USSG, 1982). Dose-response relationships are also shown for smokers whose smoking habits are like heavy passive smoking (Wynder and Goodman, 1983; Jarvis and Russell, in press), i.e., in cigarette smokers who do not inhale, and in pipe and cigar smokers, who also are unlikely to inhale (USSG, 1982; USSG, 1979).

4. Reductions in lung cancer incidence for reduction in exposure have been found in all major studies of active smoking (USSG, 1982). The one study of passive smoking and lung cancer which examined this question also found a similar result (Hirayama, 1983b). Furthermore, the comparison of the SDAs who never smoked, and who should have reduced exposure relative to the non-SDAs who never smoked, also appears to exhibit this effect.

On the basis of the IARC criteria, the evidence appears to be sufficient for reasonable anticipation of an increase in lung cancer mortality from passive smoking, justifying a quantitative risk assessment. The significance of the public health risk will now be estimated.

Estimation of Total LCD Risk and a Phenomenological Exposure-Response Relationship

A phenomenological exposure-response relationship is now derived based on consistency (Hirayama, 1983b)

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of evidence provided by studies of lung cancer in nonsmokers and from our exposure assessment. The Seventh Day Adventist Study by Phillips *et al.* (1980a, 1980b) appears to provide the best evidence of the magnitude of the lung cancer effect from passive smoking among U.S. nonsmokers.

A calculation (Appendix C) based on the age-standardized differences in lung cancer mortality rates between SDAs who never smoked and demographically comparable non-SDAs who never smoked (age groups 35 to 85+) from the studies of Phillips *et al.* (1980a, 1980b) yields an estimated 4700 lung cancer deaths (LCDs) for the 62.4 million U.S. nonsmokers (USDC, 1980) at risk (USSG, 1979) aged ≥ 35 yr. This in turn yields a passive smoking risk rate of 7.4 LCDs per 100,000 person-yr (4700 LCDs/yr per 62,424,000 persons), in good agreement with the value of 6.8 per 100,000 person-yr reported in the Hirayama (1981) study. To place the estimated mortality in perspective, 4700 deaths was about 5% of the total annual LCDs, and about 30% of the LCDs in nonsmokers in 1982 (USSG, 1982).

The exposure of nonsmokers in the U.S. population of working age, taken from the model results in Table 1, appears to be a weighted average of about 1.43 mg of tobacco tar per day, including the estimated 14% of the population who received no exposure at home or work. The carcinogenic risks will be assumed to apply even to retired persons, whose exposures are reported to be less than the employed (Friedman *et al.*, 1983), because the risks of lung cancer from smoking decline only slowly even with total cessation of exposure (USSG, 1982), and because the risks of lung cancer increase exponentially with age (NCI, 1966).

Using the statistical risk of 7.4 LCDs per 100,000, and dividing by the average exposure of 1.43 mg/day, we estimate a phenomenological exposure-response relation appropriate for the general U.S. population at risk of about 5 LCDs per 100,000 person-yr at risk per 1 mg/day nominal exposure.

The range in nominal exposure has been estimated to be 0–14 mg/day (Repace and Lowrey, 1980). Studies of lung cancer and passive smoking across three cultures have shown an exposure-response relationship. Thus, the assumption of an exposure-response relationship is justified; and a linear exposure-response function (Doll and Peto, 1981; IRLG, 1979; U.S. EPA, 1979; Crump *et al.*, 1976) is assumed. With zero excess risk from tobacco smoke for zero exposure, and applying the exposure-response relationship derived above, with the maximum exposure of 14 mg/day, a maximum risk of about (14 × 5) = 70 LCDs per 100,000 person-yr is estimated for the most-exposed lifestyle. This lifestyle has been previously typified by that of a nonsmoking musician who performs regularly in a smoky nightclub and who resides in a small apartment with a chainsmoker; many other scenarios may be drawn (Repace and Lowrey, 1980).

Estimated Loss of Life Expectancy

Reif (1981a, 1981b) argues that there exists a genetically determined distribution in natural susceptibility to lung cancer in people; the effect of exposure to tobacco smoke is to shift this distribution toward death at earlier ages. In other words, exposure to tobacco smoke produces a loss of life expectancy. One method of presenting risk data involves calculation of the loss of life expectancy, in units of days of life lost per individual, averaged over the entire population at risk. When the average life-loss is multiplied by the number of individuals at risk, the impact of the hazard on society in person-yr of life lost can be assessed. More important, one can display the age-specific probabilities of death from the hazard, as well as the average number of years of life lost by the average victim. Appendix C gives the method of calculation.

Averaged over all of the population at risk, (i.e., including those who die of other causes), the average loss of life expectancy from passive smoking is calculated (appendix C) to be 15 days, which is equivalent to an ultimate loss of 2.5 million person-yr of life for the total at-risk U.S. population in 1979 over 35 yr of age (62.4 million persons). The estimated worst-case loss of life expectancy is 148 days, again averaged over all of the population at risk. The estimated mean life expectancy lost by a passive-smoking lung cancer *victim* is 17 ± 9 yr.

How does the calculated average loss of life expectancy for heavy passive smoking compare with the average loss of life expectancy found in active smokers? The modeled worst-case lifestyle might be reasonably expected to have lesser exposure, and hence lesser risk than active smokers. Table 3, adapted from Cohen and Lee (1979), gives this comparison. The estimated most-exposed lifestyle has about ⅔ the loss of life expectancy of the average pipe smoker, about ½ the loss of the

Table 3. Estimated loss of life expectancy from active smoking (all causes) and passive smoking (lung cancer only), adapted from Cohen and Lee (1979).

Cause	Days
Cigarette smoking – male	2250
Cigarette smoking – female	800
Cigar smoking	330
Pipe smoking	220
Passive Smoking[a] (est. most exposed lifestyle)	148
Passive smoking[a] (est. average lifestyle)	15

[a]Estimated this work (see Appendix C); averaged over all nonsmokers at risk, i.e., those who are presumed to die from passive smoking-induced lung cancer, and those who do not. Estimates given for passive smoking are phenomenological estimates.

average cigar smoker, and $\frac{1}{10}$ of that for active cigarette smoking.

Estimate of an Exposure-Response Relationship Based on Risks in Smokers

An alternative extrapolated exposure-response relationship is now derived from evidence provided by studies of lung cancer in cigarette smokers. Using the Surgeon General's estimate that 85% of all lung cancers are due to smoking (USSG, 1982), a current annual LCD rate to smokers at risk of about 316 per 100,000 is estimated (see Appendix B). Assuming a one-hit model (see Appendix B) for extrapolation of the risk (which in this range is functionally equivalent to the linear assumption that a milligram of tobacco tar inhaled by a nonsmoker produces a response equivalent to that in a smoker) yields an estimate of about 0.87 LCDs/100,000 person-yr. This corresponds to an exposure-response relationship of 0.6 LCDs/ 100,000 person-yr per mg/day, and an annual aggregate risk estimate of about 555 LCDs per year, an order of magnitude lower than the phenomenological estimate.

Discussion of Alternative Exposure-Response Relationships

We now speculate on why these two different methods produce such disparate estimates of risk. One possibility is that nonsmokers may have a reduced tolerance to the effects of tobacco smoke. Another possibility is a "large dose" effect (Jarvis and Russell, in press), whereby exposure to tobacco tar at the lesser doses experienced by nonsmokers produces a greater risk per unit dose than the greater doses experienced by active smokers, whose lung tissue is saturated by carcinogenic tar. Large dose effects have been observed in cancer induction by ionizing radiation, in which the dose-response curve has a linear form at low doses, a quadratic upward (positive) curvature at intermediate doses, but a downward (negative) curvature at high doses (NRC, 1980). Downturns in exposure-response curves of lung cancer in smokers of more than 40 cigarettes per day have been observed by Doll and Peto (1978) and Hirayama (1974). The effect of a leveling-off or downturn in the exposure-response curve at large exposures would be to cause a linear model to underestimate the risk when extrapolated (Hoel *et al.*, 1975, 1983; NRC, 1980) over two orders of magnitude to low exposures.

A third possibility is generated by modeling the dose, as opposed to the exposure, of nonsmokers to tobacco smoke. Nonsmokers' exposure is translated into dose by means of a simple single-compartment model for lung deposition and clearance (Repace, 1983). This model suggests that tar may accumulate on the surface of nonsmokers' lungs to an equilibrium dose an order of magnitude higher than the nominal exposure, to a level of about 16 mg/day, due to the long pulmonary residence times for respirable aerosols. If this 16-mg dose, rather than the 1.4-mg exposure, is the operative factor, then the typical passive smoker would have a risk, according to the one-hit model, of about 9 per 100,000, in agreement with the phenomenological estimate.

There is support for this argument from Matsukura's study (1984), which showed that heavy passive smokers had urinary cotinine levels comparable to active smokers of less than 3 cigarettes per day, and from Kasuga's study (1983), which also showed that heavy passive smokers had urinary hydroxyproline levels almost equivalent to that of light smokers. Moreover, similar observations have been found indicating that serum thiocyanate (Cohen and Bartsch, 1980) and benzpyrene (Repetto and Martinez, 1974) levels in some passive smokers were comparable to the elevated levels typically found in smokers.

The simple model we have proposed ignores the effect of cancer latency. The long latency period for lung cancer indicates that childhood passive smoking may be an important factor affecting risk in adult life: Doll and Peto (1981) have suggested that the effect of passive smoking may be surprisingly large because lifelong exposure may produce a lung-cancer effect four times as great as that which is limited to adult life (recall the observation of Sandler *et al.*, in press: childhood passive smoking appeared to elevate the cancer risk of adults). As Bonham and Wilson (1981) have shown from a national study of 40,000 children in 1970, 62% came from homes with one or more smokers, indicating that many adults receive exposure during childhood.

Sensitivity Analysis

Which of the two exposure-response relationships derived is more useful in explaining actual epidemiological data? The Garfinkel (1981) American Cancer Society (ACS) study of passive smoking and lung cancer, which spanned the years 1960 to 1972, reported a standardized mortality ratio of 1.20 and an annual lung cancer rate of 13.3 per 100,000 person-yr. Of the 176,739 women in the Garfinkel study, 28% had nonsmoking husbands. Thus, the "controls" numbered 49,487 and the total "exposed" were 127,252. According to census data (U.S. Dept. of Commerce, 1980), female participation rates in the labor force ranged from 37.1% in 1960 to 38.8% in 1965, 42.8% in 1970, and 43.7% in 1975, and were about 80% of the 1965 level in 1947. Thus, it appears that about 38% of the women in this study were in the labor force, and presumably exposed to passive smoking while at work. It is assumed that for both groups of women, control and exposed, 38% were employed and exposed to ambient tobacco smoke while at work.

As indicated in Table 1, typical U.S. nonsmoking

Group	Number
Total cohort	176,739
"True" controls; do not work, husbands do not smoke	30,682
"Tainted" controls: work, husbands do not smoke	18,805
Total "controls"	49,487
"Exposed" workers: work, husbands smoke	48,356
"Exposed" nonworkers: do not work, husbands smoke	78,896
Total "exposed"	127,252

adults are estimated to inhale 1.82 mg of tobacco tar per average day at work and 0.45 mg per average day at home, an exposure ratio of 4:1. This occurs because, although domestic and workplace air exchange rates are similar (Appendix A), workplace smoker densities tend to be far higher. Let the assumed basal rate of lung cancer deaths in these women from causes other than passive smoking be 8.7 per 100,000 (the age-adjusted rate for nonsmoking women married to nonsmokers in Hirayama's study, 1981a). The Garfinkel (1981) ACS cohort can now be broken down as shown in Table 4.

The Garfinkel (1981) study can be analyzed as follows, using the phenomenological exposure-response relationship of 5 LCDs/100,000 person-yr-mg/day.

The lung cancer deaths per 100,000 contributed by passive smoking are then 2.25 (0.45 × 5) for the home and 9.10 (1.82 × 5) for the workplace. Application of these figures to the numbers of true and tainted controls and working and nonworking exposed women yields, after addition of the basal risk of 8.7 per 100,000, the estimated rates for lung cancer deaths per 100,000 person-yr, as shown in Table 5. The ratio of risks (all exposed:all controls) is thus 1.19. The ratio (averaged over husbands' heavy and light smoking categories) in the Garfinkel (1981) study was 1.20, less than a 1% difference. The lung cancer death rate for the weighted average of the "exposed" and "control" categories is 13.8 per 100,000. Over the 12 yr of the Garfinkel study, the actual rate averaged 13.3 per 100,000, a less than 4% difference. In other words, this analysis (Repace, 1984) appears to explain both the observed lung cancer death rate and observed risk-ratio of the Garfinkel ACS cohort.

Could this be due to chance? Suppose that, instead of 36% of women in the workforce, 100% of women lung cancer death rate would be 19.42, a 46% difference. Suppose 0% of women worked. Then the ratio of risks would be 1.26, a 5% difference from Garfinkel's result, but the lung cancer death rate would be 10.32 per 100,000, a 22% difference from Garfinkel's observation.

Suppose the exposure-response relationship of 0.6 LCDs/100,000 person-yr per mg/day yielded by extrapolation with the one-hit model from the risks in smokers is used. The lung cancer deaths per 100,000 contributed by passive smoking are then 0.27 (0.45 × 0.6) for the home and 1.1 (1.82 × 0.6) for the workplace. Application of these figures to the numbers of true and tainted controls and working and nonworking exposed women yields, after addition of the basal risk of 8.7 per 100,000, the figures shown in Table 6. The ratio of risks (all exposed:all controls) is then 1.03. Compared with the risk ratio in the Garfinkel (1981) study, this is a 14% difference. The lung cancer death rate for the weighted average of the "exposed" and "control" categories is 9.3 per 100,000, a 30% difference from Garfinkel's result.

When the one-hit model is used, the ratio of "all-exposed" to "true" controls is 1.09, a 38% difference with Hirayama's ratio. The corresponding lung cancer mortality rate is 9.45, a 39% difference with Hirayama's result.

Finally, using the phenomenological exposure-response relation, the ratio for "all exposed" and "true" controls is 1.7. Hirayama's (1981) average risk ratio was 1.78 from passive smoking, a 4.5% difference. Furthermore, if lung cancer risk rate calculation is performed with the tainted controls included as an exposed group, the result is 14.8 per 100,000, compared with Hirayama's observed 15.5 per 100,000, a 4% difference. In other words, the effect of moving the confounding tainted controls from Garfinkel's control group into his exposed group is to yield results within 5% of Hirayama's.

Thus, on the basis of this sensitivity analysis, it would appear that the phenomenological exposure-response relationship is better able to describe the results of the Garfinkel (1981) study than the one-hit model, and in addition, also appears to be able to explain quantitatively why the two large prospective studies of passive smoking and lung cancer yielded different results.

Table 5. Calculated lung cancer risks for each subgroup in the Garfinkel (1981) study using the 5 LCDs/100,000 person-yr/mg/day exposure-response relation.

Group	Rate
True controls	8.7
Tainted controls	17.8 (8.7 + 9.1)
All controls (weighted mean)	12.16
Exposed workers	20.05 (8.7 + 2.25 + 9.10)
Exposed nonworkers	10.95 (8.7 + 2.25)
All exposed (weighted mean)	14.41

Table 6. Calculated lung cancer risks for each subgroup in the Garfinkel (1981) study using the 0.6 LCDs per 100,000 person-yr/mg/day exposure-response relation.

Group	Rate
True controls	8.7
Tainted controls	9.8 (8.7 + 1.1)
All controls (weighted mean)	9.11
Exposed workers	10.07 (8.7 + 0.27 + 1.1)
Exposed nonworkers	8.97 (8.7 + 0.27)
All exposed (weighted mean)	9.39

Table 7. Comparison of estimated risks from various hazardous air pollutants. Risks have been assessed for non-occupational exposures of the general population to several hazardous air pollutants. All are airborne carcinogens; all but passive smoking are being regulated by society. The statistical mortality given is before control.

Pollutant	Estimated Annual Mortality[a,b]	Reference
Passive smoking	5000 LCDs per yr	(this work)
Vinyl chloride	<27 CDs per yr	(U.S. EPA, 1975)
Radionuclides (worldwide impact from Department of Energy facilities)	17 CDs per yr	(U.S. EPA, 1983b)
Coke oven emissions	<15 LCDs per yr	(U.S. EPA, 1984)
Benzene	<8 CDs per yr	(U.S. EPA, 1979b)
Arsenic	<5 LCDs per yr	(U.S. EPA, 1980)

[a]CD = cancer death; LCD = lung cancer death.
[b]Risks for passive smoking and radionuclides are best estimates, and risks for other pollutants are upper bound.

Comparison of the Estimated Risk of Passive Smoking with those of Hazardous Air Pollutants Currently Under Regulation

Although the quantitative estimates presented should be regarded as preliminary and subject to confirmation by further research, the evidence suggests that passive smoking appears to be responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers. To place these estimates in perspective, Table 7 gives a comparison of the estimated risk of passive smoking to risks estimated by the U.S. Environmental Protection Agency for the carcinogenic hazardous air pollutants currently regulated under section 112 of the Clean Air Act (SCEP, 1977). As Table 7 demonstrates, passive smoking appears to pose a public health risk larger than the hazardous air pollutants from all regulated industrial emissions combined.

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Appendix A: Modeling Exposure of Nonsmoking U.S. Adults to Ambient Tobacco Smoke

Introduction

Lifestyle is the integrated way of life of an individual; aspects of lifestyle which will be considered here have to do with the amount of time a nonsmoker spends in contact with smokers, and therefore with their effluent. Exposure of nonsmokers to tobacco smoke might be expected to be common in the United States because one out of three U.S. adults smokes cigarettes at the estimated rate of 32 per day (Repace and Lowrey, 1980), and an additional one out of six smokes cigars or pipes. Furthermore, indoor air pollution from tobacco smoke persists in indoor environments long after smoking ceases (Repace and Lowrey, 1980, 1982).

Earlier work (Repace and Lowrey, 1980) presented a model of nonsmokers' exposure to the particulate phase of ambient smoke which was supported by controlled experiments and field survey of the levels of respirable particles indoors and out, in both smokefree and smoky environments. This work, which established that ambient tobacco smoke imposed significant air pollution burdens on nonsmokers, was extended by later work (Repace and Lowrey, 1982) that further demonstrated the predictive power of this model. The model predicts a range of exposure of from 0 to 14 mg of cigarette aerosol per day, depending upon the nonsmoker's lifestyle. Exposures of prototypical nonsmokers were modeled, but no attempt was made to estimate the average population exposure. Concentrations of ambient tobacco smoke encountered by nonsmokers can be approximated by equilibrium values that are determined by the ratio of the average smoker density to the effective ventilation rate (Repace and Lowrey, 1980, 1982); in practice, design ventilation standards based on occupancy are useful surrogates for effective ventilation rates. On the average, a characteristic value of this ratio can be assigned to a particular microenvironmental class, e.g., homes, offices, restaurants, etc. (Repace *et al.*, 1980). Therefore, the average daily exposure of individuals can be estimated from the time-weighted sum of concentrations encountered in various microenvironments containing smoke (Ott, in press; NRC, 1981; Szalai, 1972; Repace *et al.*, 1980).

Exposure and lifestyle

It is important to realize that most persons' lifestyles are such that they spend nearly 90% of their time in just two microenvironmental classes, thus affording a great simplification of exposure modeling. Szalai (1972), as part of The Multinational Comparative Time Budget Research Project, which studied the habits of nearly 30,000 persons in 12 countries (from 1964 to 1966), has compiled data reporting the average time spent in various locations or microenvironments. The data for 44 cities in the United States, as analyzed by Ott (in press) are summarized in Table A1 (see also NRC, 1981).

Table A1 shows that U.S. urban people spend an average of 88% of their time in just two microenvironments: in homes and workplaces. Moreover, employed persons in the U.S. cities are estimated to spend only 3% of the day outdoors, while housewives spend only 2% outdoors (Ott, in press; NRC, 1981). Assume that these values are representative of the entire population. [In 1970, approximately three fourths of the population was urban (USDC, 1980).]

Table A1. Time spent in various microenvironments by persons in 44 U.S. cities, expressed in average hours per day. (Ott, in press; NRC, 1981; Szalai, 1972).

Microenvironment	Employed Men, All Days	Employed Women, All Days	Married Housewives, All Days
Inside one's home	13.4	15.4	20.5
Just outside one's home	0.2	0.0	0.1
At one's workplace	6.7	5.2	–
In transit	1.6	1.3	1.0
In other people's homes	0.5	0.7	0.8
In places of business	0.7	0.9	1.2
In restaurants and bars	0.4	0.2	0.1
In all other locations	0.5	0.3	0.3
Total	24.0	24.0	24.0

Modeling exposure of nonsmokers at work

Exposure of the population to the particulate phase of cigarette smoke can be modeled to determine both range of exposure and the nominal inhaled dose, which is exposure multiplied by the respiration rate (Altman and Dittmer, 1974).

Repace and Lowrey (1980, 1982a) have shown that the ambient concentration of tobacco smoke particles, Q, from cigarette smoking can be usefully represented by an equilibrium model of the form $Q = 650\, D_s/C_v$ where D_s is the number of burning cigarettes per 100m³, and C_v is the ventilatory air exchange rate in air changes per hour (ach). Rewriting this in terms of the occupancy of the space by habitual smokers (Repace and Lowrey, 1980) (for every 3 habitual smokers, there is one cigarette burning constantly), $D_{hs}(= 3D_s)$:

$$Q = 217\, D_{hs}/C_v \quad (\mu g/m^3), \qquad \text{(A1)}$$

where D_{hs} is the habitual smoker density in units of smokers per 100 m³, and C_v is the air change rate in units of air changes per hour (ach). Because The American Society of Heating, Refrigerating, and Ventilating Engineers (ASHRAE) (Leaderer *et al.*, 1981), sets consensus standards for ventilation rates in the United States, and because those standards are tied to expected building occupancy (e.g., ASHRAE, 1981), Eq. (A1) offers the possibility of modeling the range of nonsmokers' exposures by estimating the ranges of occupancy and air change rate. Appendix A1 estimates that the average annual exposure to ambient tobacco smoke particles by a typical nonsmoking U.S. worker is 1.8 mg/day, with an exposure probability of 63%.

Modeling exposure of nonsmokers at home

By reviewing data from time budget and census studies, the average length of time a person spends in the home microenvironment can be calculated. This time differs for gender and employment status. Taking into account the different amounts of time spent in the home by employed men, employed women, and home-makers, an estimate of occupancy-weighted average number of cigarettes smoked in the home during a 16-h waking day can be made. If the entire waking day is spent at home, 32 cigarettes per day (CPD) are smoked in the house by a smoker of either sex. An estimated occupancy-weighted average number cigarettes equal to 22 CPD smoked in the typical home is derived in Appendix A2. Using Eq. (A1), multiplied by the ratio 22/32, times a 1 m³/h respiration rate for a 16-h period, the calculation is made for a single-family detached dwelling of 340 m³ volume (see Appendix A3), assuming that on a 16-h basis, the entire finished volume of the home is available for dispersion of the smoke. A typical nonsmoker of either sex appears to be exposed to an average inhaled dose of 0.45 mg/day, assuming that occupancy of the home by smokers and nonsmokers is coincident.

Mean estimated dose to a typical adult from the most-frequented microenvironments

A probability-weighted average exposure to a hypothetical typical U.S. adult is estimated by combining the estimated dose to U.S. adults exposed in the workplace and at home, and by weighting the exposure received in each microenvironment by the probability of receiving it. Appendix A1 estimates that nonsmoking U.S. workers are exposed on the job to tobacco smoke with a probability of 63%. Appendix A2 estimates that nonsmoking U.S. adults are exposed at home to tobacco smoke with a probability of 62%. Table 1 (main text) gives the combinations of these probabilities, assuming that they are independent, i.e., that exposure at work is not correlated to exposure at home. Table 1 suggests that only a relatively small percentage (14%) of the population may escape daily passive smoke exposure. By contrast, individuals having exposure both at home and at work constitute a high exposure group, with the workplace likely contributing more exposure than the home by a ratio of 4 to 1.

On the basis of Table 1 it is estimated that the mean daily exposure of nonsmoking U.S. adults to tobacco tar and nicotine from the breathing of indoor air contaminated by cigarette smoke is about 1.43 mg/day, averaged over the two most-frequented microenvironments. This may be compared to the estimate of 14 mg/day to the hypothetical most-exposed individual (Repace and Lowrey, 1980). These results indicate that the typical U.S. "nonsmoker" appears to be exposed to a finite, non zero amount of tobacco aerosol, equivalent in value to three low-tar cigarettes (0.55 mg) per day.

In summation, it is possible, based on ASHRAE standards, time budget, and census surveys, the physics of indoor air pollution transport, and tables of respiration rates, to estimate the average exposure of a typical nonsmoking U.S. adult of working age. Using this methodology, estimates of the average exposure of the U.S. adult population of working age to the particulate phase of ambient tobacco smoke are made for the two most-

frequented microenvironments: the workplace and the home. It is estimated that 86% of adults of working age are exposed to ambient tobacco smoke on a daily basis, and 14% are not. It is estimated that the range of exposure varies from 0 to 14 mg of tobacco tar per day, and that the typical exposure, averaged over 100% of the population, is 1.43 mg/day. It also is estimated that those individuals who are exposed both at home and at work receive a daily average exposure of 2.4 mg/day, and that 39% of the adult worker population is in this category. Those individuals exposed *only* at home receive a daily exposure of 0.5 mg/day, and that 23% of the adult population is in this category. Finally, it is estimated that those individuals exposed *only* at work receive a daily exposure of 1.8 mg/day, and that 24% of the worker population is in this category. Thus these estimates suggest that the ratio of workplace dose to the exposure received at home is nearly 4:1, indicating that, on the average, the workplace is a more important source of exposure than the home environment. Consistency of these estimates of workplace and domestic exposure with field data is given in Appendices A1 and A2.

Appendix A1: Modeling the Average Daily Exposure to Cigarette Smoke for a Typical U.S. Nonsmoking Worker

It is possible to arrive at an estimated aggregate exposure because the range of occupancies (i.e., smoker densities) is tied to the range of ventilation rates, which in turn determine the range of concentration of ambient tobacco smoke to which nonsmokers are exposed. A form of Eq. (A1) is given that can be related directly to the ASHRAE Standards 62-73 (ASHRAE, 1973), promulgated in 1973, which set standards for natural and mechanical ventilation. The practical range of occupancy given in the ASHRAE Standard 62-1973 is from 5 persons/1000 ft^2 to 150 persons/1000 ft^2 (5.4 P/100 m^2 to 161 P/100 m^2), for commercial and institutional buildings.

From 1946 to 1973, the operable engineering standard was descriptive of general practice rather than prescriptive: The American Standard Building Code Requirements for Light and Ventilation A53, Section 8 (ASA, 1946) described typical practice for mechanical ventilation based on floor area, not occupancy. Section 8 described minimum values of 0.5 CFM/ft^2 for offices, 1 to 1.5 CFM/ft^2 (4.4 to 6.6 L/s m^2) for workrooms, and a range of 0.05 to 3 CFM/ft^2 (2.2 to 13.2 L/s m^2) for public and institutional buildings, with the lower value applying to museums, and the upper value to dance halls. This implies air exchange rates varying from 3 to 18 ach, and at the maximum of 75% recirculation described, this range reduces to 0.75 to 4.5 ach. In 1970, 60.7% of the U.S. workforce worked in the white-collar and service occupations that inhabit such buildings (USDC, 1980). A 1979 survey of 3000 employers in large, medium, and small corporations indicated that smoking was prohibited in only 10.5% of white-collar workplaces and in 27.5% of blue-collar workplaces (NICSH, 1978). These percentages would likely have been less in 1970. Equation (A2) expresses the concentration, R, as a function of occupancy, which is now a surrogate (Repace and Lowrey, 1978, 1982a) for smoker density:

$$R = 25.6\, P_o/C_v \quad (\mu g/m^3), \qquad (A2)$$

where P_o is the occupancy in persons per 1000 ft^2 [100 m^2], and C_v is the ventilatory air change rate in ach, as before. Exposures can be calculated by multiplying R by the integrated average respiration rate expected for an adult nonsmoker over an 8-h workday. A reasonable value is 8 m^3 per workshift, a value corresponding to alternate sitting plus light work (Table A2). Multiplying Eq. (A2) by this rate yields the equation for the amount of tobacco tar inhaled, N_d:

$$N_d = 0.205\, P_o/C_v \quad (\text{mg}/8\ \text{h}), \qquad (A3)$$

where the other parameters are defined as in Eq. (A2). ASHRAE Standards 62-73 yield the ranges in P_o of 5 to 150 and in C_v of 0.15 to 18 ach.

Table A3 expresses the variation of these parameters from the absolute minimum airchange rate to the recommended minimum and maximum rates, and enables us to bound the modeled dose for the workplace. The extreme bounds of workplace exposure can be estimated to range from $1.35 \le N_d \le 6.77$ mg/8 h. This assumes that one-third of the occupants are smokers [following the U.S. average that one-third of the adult population smokes (USSG, 1979)], and that they smoke sales-weighted-average tar cigarettes at the rate of 32 per 16-h day (Repace and Lowrey, 1980). Clearly, the true minimum bound is zero, and the maximum exposure may be higher due to the presence of chainsmokers or a higher than average number of smokers, but what is desired is an expected average value for the workplace exposure. At the ASHRAE-recommended minimum ventilation, the upper bound for N_d will be 3.38 mg/8 h. Thus, the probable average range for N_d is between 1.35 and 3.38 mg/8 h. The average of these two figures, N_d = 2.37 mg/8 h, represents the mean exposure for U.S. workers who are on-the-job passive smokers. This value may be

Table A2. Range of typical adult respiration rates for different levels of effort after Altman and Dittmer (1971).

Activity Level	Respiration Rate (m^3/h)
Resting	0.36
Sitting	0.60
Alternate Sitting & Light Work	0.99
Light Work	1.47
Heavy Work	2.04

Table A3. Calculation of the range of concentration Q, and exposure N_e to which nonsmokers are subject under the model given by Eqs. (A2) and (A3) assuming ASHRAE standard ventilation.

Occupancy	P, [occupants per 1000 ft² (per 100 m²)]	C, [airchanges/hour (ach)]	N_e Exposure (mg/8 h)	Q Concentration (μg/m³)
A. Using ASHRAE 62-73 recommended maximum makeup air based on occupancy				
Maximum	150	18	1.69	213
Minimum	5	0.5	2.03	256
Offices	10	1.5	1.35	170
B. Using ASHRAE 62-73 absolute minimum makeup air based on occupancy				
Maximum	150	4.5	6.77	853
Minimum	5	0.15	6.77	853
Offices	10	0.3	6.77	853
C. Using ASHRAE 62-73 recommended minimum makeup air based on occupancy				
Maximum	150	9	3.38	655
Minimum	5	0.3	3.38	655
Offices	10	0.9	2.26	284

transformed into a daily average using Table A1. In 1972, (USDC, 1980) 38% of the workforce was female: 0.38 × (5.2 workhours/day) and 62% was male: 0.62 × (6.7 workhours/day); the sum of these is 6.13 workhours/day, daily average. Thus, the daily average exposure is N_e = (6.13/8) × 2.37 = 1.82 mg/day.

It now remains to estimate the percentage of workers who are exposed to cigarette smoke at work. The National Interagency Council on Smoking and Health conducted a survey of top management and health officials of 3000 U.S. corporations in 1978 (NICSH, 1978). A 29% response rate was achieved. The survey indicated that of blue-collar companies surveyed, 30.6% had no restrictions on smoking, 42% permitted smoking in designated areas, and 27.5% completely prohibited smoking. The corresponding percentages for the white-collar companies were, respectively, 74.3%, 15.2%, and 10.5%. Smaller companies were less likely to have restrictions. Among companies with restrictions, about one-half imposed penalties for violations. In addition, 65% of the respondents indicated that their policy was established after the release of the 1964 Surgeon General's Report on Smoking.

In 1970, white-collar workers constituted 48.3% of the workforce, blue-collar workers 35.3%, service workers 12.4%, and farmworkers 4% (USDC, 1980). The largest change in any category from 1960 to 1979 was that of white-collar workers, increasing by 7%. Since about one-half of the blue-collar companies imposed penalties for smoking, it will be assumed that 50% of the blue-collar nonsmokers were not exposed on the job. By contrast, it will be assumed that only 25% of the white-collar workers were not exposed. It will further be assumed that one-half of all workers follow white-collar smoking rules, and the other half, consisting of blue-collar workers, service workers, and farmworkers, follow blue-collar rules. Thus, the estimated weighted average percent of nonsmoking workers who are significantly exposed to tobacco smoke on the job is: 0.50 × 50% + 0.75 × 50% = 62.5%. By comparison, a 1983 survey of 1515 white-and blue-collar businesses sampled at random reported that "nearly two-thirds" had no smoking restrictions in the workplace (Tobacco Institute, 1984).

At this stage it must be asked whether the numbers calculated are reasonable in terms of measurements of ambient tobacco smoke under natural conditions. Repace and Lowrey (1980, 1982a), in a field survey of ambient tobacco smoke in 23 commercial buildings in the metropolitan Washington, D.C., area during 1979–1980, found concentrations ranging from about 100 μg/m³ to more than 1000 μg/m³. This range is quite compatible with the concentrations Q derived in Table A3. The average of all values measured under a variety of smoking conditions and ventilation rates by Repace and Lowrey was 242 μg/m³ (range 100 to 1000 μg/m³) for these 23 locations, corrected for background. This is compatible with the values calculated in Table A3. Breathing 242 μg/m³ of ambient tobacco smoke for 8 h at a rate of 0.99 m³ h yields an exposure of 1.92 mg/8 h or on a daily average basis, 1.92 × (6.13/8) = 1.47 mg.

In terms of relative exposures, these results also appear to be reasonable. In Appendix A2, an average smoking rate of 32 CPD was used (Repace and Lowrey, 1980). At current sales-weighted average tar plus nicotine values (14 mg) (USFTC, 1984), the typical smoker would inhale (14 mg/cig) × 32 CPD = 448 mg/day. In Table 1, the typical passive smoker was calculated to inhale 1.43 mg/day. This is a relative exposure ratio of 313:1. Wald *et al.* (1984a), in a study of urinary cotinine levels in smokers and nonsmokers, found the ratio (1645 ng/mL)/(6 ng/mL) = 274:1. Thus, the ratio of exposures calculated theoretically using the model derived here differs by only 14% from an experimentally derived value based on a biological marker of exposure.

Appendix A2. Calculation of the Estimated Daily Average Number of Cigarettes Smoked in the Average Home

Since the source strength depends upon the length of time smokers spend in indoor microenvironments, it is necessary to review pertinent information from time budget (Ott, in press; Szalai, 1972; NRC, 1981) and census (USDC, 1980) studies, which gives the average length of time that persons spend in various microenvironments.

From Table A1, it is seen that, allowing for 8 h of sleep, employed men spend 34.4% of the waking day in

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the home; employed women spend 45.9% of the waking day in the home; "housewives" spend 81% of the waking day in the home. In 1979, approximately 42% of families with both the husband and wife present, both were employed. Thus for homes occupied by married couples, 66% of the waking day (weighted mean averaged over 42% working wives and 58% homemakers) the home is occupied by a wife, and 34% of the day, by a husband. If the average habitual smoker smokes 32 cigarettes per day (CPD), then the wife will smoke 21 CPD in the house, and the husband will smoke 11 CPD in the house.

Bonham and Wilson (1981) found that 62% of U.S. homes with children in 1970 contained one or more smokers, and 25% contained two or more. Thus we may assume that of homes with one or more smokers, 40% have two smokers, and 60% have one smoker. We have three cases to consider: (a) Husband and Wife Both Smoke, (b) Only Wife Smokes, and (c) Only Husband Smokes. In 40% of the smoking homes, case (a) is true, and in 60% of those homes, either cases (b) or (c) is true. Specifically, 38% of men and 30% of women smoke (US DHHS, 1979). Then the probability of case (c) being true is 34% (38/68 × 60%), and the probability of case (b) being true is 26% (30/68 × 60%). The weighted mean of these is given by the sum of the products of the percent of homes with a given number of smokers of either or both sexes, times the number of cigarettes per day smoked by either or both sexes: $0.40 \times 32 + 0.26 \times 21 + 0.34 \times 11 = 22$ CPD, estimated to be smoked daily in the average U.S. home, or about a pack per day. Is this theoretical estimate a reasonable number?

Dockery and Spengler (1981a, 1981b), in a 1-yr study of indoor air pollution in 68 homes in 6 U.S. cities, found that cigarette smoking was the dominant source of respirable particles (RSP); in a typical house in the study, the average 24-h RSP levels were increased by 0.88 $\mu g/m^3$ per cigarette smoked, and in a tightly sealed house, by a value of 2.11 $\mu g/m^3$. At an estimated occupancy-weighted average in-the-home smoking rate of 22 cigarettes per day, a 24-h average RSP level of about 19 $\mu g/m^3$ (22 CPD × 0.88 $\mu g/m^3$ CPD) is calculated for the typical house; in fact, Spengler *et al.* (quoted in NRC, 1981) observed a 24-h average of 19 $\mu g/m^3$ in 22 of the homes in the study where there was only 1 smoker. This number corresponds to an air exchange rate of 1.5 ach using the model (see Appendix A3). Since this air exchange rate is within the expected range (Repace and Lowrey, 1980, 1982), an average of 22 CPD smoked in the home provides a reasonable basis for estimating exposure.

The theoretical in-the-home number of cigarettes smoked in the home is weighted for occupancy during the waking day. Since there is no data differentiating occupancy for smokers and nonsmokers, it is assumed that the statistical occupancy of the nonsmoker is coincident with that of the smoker, i.e., that there is a nonsmoker present to receive the exposure. In order to calculate the daily dose received, Eq. (A1) is used with the parameters $D_{hs} = 0.29$ smokers/100m³, $C_v = 1.5$ ach, times an occupancy factor of 22/32, times a respiration rate of 0.99 m³/h, times a 16-h maximum exposure day, yielding an estimated average exposure of 0.45 mg/day, for an adult nonsmoker, with an exposure probability of 62%.

A reasonable approximation to the probability of a typical nonsmoking adult being exposed to ambient tobacco smoke at home is 62%, the same as Bonham and Wilson (1981) above found for adults with children (in 1970, 56% of families had one or more children under 18) (USDC, 1980). No differentiation is made between male and female nonsmokers, since Friedman *et al.* (1983) observed that degree of passive smoking had little correlation with gender. In households with 2 or more smokers, there might not be an adult nonsmoker to be exposed; in this case, the probability of passive smoking (for a nonsmoker) reduces from 62% to 37%. However, the estimated total exposure (Table 1) only decreases by 8%, from 1.43 to 1.34 mg/day. In the absence of data on this point, it will be assumed that a nonsmoking adult is present.

Appendix A3. Calculation of the Ratio of the Habitual Smoker Density to the Air Exchange Rate for a Typical U.S. Single Family House

The typical range of annual closed-window air exchange rates in U.S. residences is generally considered to be of the order of 0.5 to 1.5 ach, with the range for the average residence of the order of 0.7 to 1.1 ach, and that of the tighter and newer residences of the order of 0.5 to 0.8 ach (Fuller, 1981). So-called energy-efficient structures have rates of the order of 0.3 to 0.5 ach. (Repace, 1982). A typical U.S. single-family detached house is estimated to have a floor area of 1500 ft.² [139 m²] with an 8-ft [2.4-m] ceiling, for a volume of 340 m³ (NAHB, 1981).

Thus, per habitual smoker, the ratio $D_{hs}/C_v = (1/3.4)/1.0 = 0.29$ habitual smokers per hundred cubic meters per air change per hour. In 1978, nearly ⅔ of occupied housing units were single-family detached dwellings (USDC, 1980). It is assumed that the ratio calculated above is valid for multifamily dwellings as well (the volume of an apartment in a multifamily building is likely to be less, but the air exchange rate is likely to be greater).

Appendix B: Extrapolated Estimate of Risk From Passive Smoking

An alternative method of estimation of risk from passive smoking is calculated as follows. In 1980, 108,504 individuals in the United States were reported

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to have died from lung cancer (USPHS, 1983). The 1982 Surgeon General's report on Smoking and Cancer estimated that 85% of LCDs are due to cigarette smoking (USSG, 1982); this yields 92,228 LCDs/yr. Lung cancers occur primarily in smokers over the age of 35 (NCI, 1966); in 1980, there were an estimated 29,225,000 smokers of all races and both sexes in this age bracket (USPHS, in press). It follows that in 1980, there were 3.156×10^{-3} LCDs per smoker of lung cancer age. In 1978 the average cigarette was 17 mg tar, and the average smoker smoked 32 cigarettes per day (Repace and Lowrey, 1980), for an estimated tar intake of 544 mg/day-smoker. (A 1980 lung cancer death reflects a 20- to 40-yr smoking history, during which smoking rates increased by, and tar levels decreased by, about 50% (USSG, 1979). Thus, 3.156×10^{-3} LCDs/smoker divided by 544 mg/day-smoker yields a rate of about 5.8×10^{-6} LCDs/yr per mg/day per smoker of lung cancer age.

Using a one-hit model (Hoel *et al.*, 1983; Crump, 1976) for the extrapolation of the risk from the estimated exposure of smokers down to the estimated exposure of nonsmokers provides an alternate exposure-response relationship. Crouch and Wilson (1981) have used this model, which saturates at high exposures, but which is linear at low exposures. This model has the form $P(D) = 1 - \exp(bD)$, where $P(D)$ is the estimated risk, b is the exposure-response function, and D is the exposure. The one-hit model, because of its functional form, can be considered as the first stage of the more complex multistage model. (U.S. EPA, 1983a; Hoel *et al.*, 1983) Whenever the data can be fitted adequately by the one-hit model, estimates of both models will be comparable (U.S. EPA, 1983a; Crump, 1976; Hoel *et al.*, 1983).

From above, $b = 5.8 \times 10^{-6}$ LCDs per year per mg/day. $D = 1.5$ mg/day, from the estimated average exposure for the typical U.S. nonsmoker (Appendix A), assuming that per milligram, tobacco tar produces the same carcinogenic response in nonsmokers as it does in smokers. This calculation yields an estimated annual LCD risk about 0.87×10^{-5} from passive smoking, or about an order of magnitude lower than the phenomenological estimate made earlier. In this exposure range, this result is essentially the same as would be obtained from a linear extrapolation.

The primary age group at risk of lung cancer is that $\geq$ 35 yr (Reif, 1981a, 1981b). Therefore, in the calculation that follows only nonsmokers $\geq$ 35 yr will be assumed to be at risk of lung cancer. In 1980, there were about 63.8 million nonsmokers aged $\geq$ 35 (USPHS, in press). Thus, the alternative risk estimate is derived from multiplying 0.87 LCDs/yr per 100,000 passive smokers times 63.8×10^{6} passive smokers at risk, yielding 555 LCDs per year in U.S. nonsmokers from passive smoking, using the one-hit model of carcinogenesis for extrapolation.

Appendix C: Age-Standardized Calculation of Estimated Annual U.S. Mortality and Loss of Life Expectancy From Involuntary Exposure to Ambient Tobacco Smoke

Approximately 50% of SDAs in the cancer age range (>35 yr old) are adult converts to the church; others were either born into an SDA home or joined the church prior to age 20, typically with other immediate family members. A large proportion of SDAs tend to be heavily involved in church activities. Only a small proportion of SDAs report current use of cigarettes (males, 1.7%; females 0.5%) (Phillips *et al.*, 1980b). (By contrast, in 1970, 43.5% of adult males and 31.1% of adult females in the general population aged $\geq$ 17 yr reported smoking) (USDHHS, 1979).

Moreover, a substantial portion of SDAs work for "an organization owned and operated by the SDA Church" [nearly 45% of SDA females and 40% of SDA males in the study group (aged $\geq$ 25 yr), reported working for the SDA Church.] (Phillips *et al.*, 1980a, 1980b). Clearly, SDAs are less likely than the general population to be involuntarily exposed to tobacco smoke, as children or as adults, at home or in the workplace, because neither SDA homes nor SDA businesses are likely to be places where smoking is permitted, and because the great majority of SDA family and social contacts are among other SDAs who do not smoke (Phillips *et al.*, 1980b).

Table C1 shows the age-standardized calculation of estimated loss of life expectancy and annual lung cancer mortality from passive smoking. The calculation is based on the lung cancer mortality difference between two Southern California cohorts of self-reported nonsmokers who never smoked. Based on lifestyle differences, they appear to have different average levels of involuntary smoke exposure. The more-exposed group are designated non-SDAs, and the less-exposed group SDAs (see main text).

Columns 1, 2, 5, and 6 are tabulations from which age-adjusted mortality rates were calculated in the study of mortality in the Seventh-Day Adventist (SDA) by Phillips *et al.* (1980a, 1980b). Columns 1 and 2 and 5 and 6 give the age-specific lung cancer deaths and person-years at risk, respectively, for the SDA and the non-SDA. The fractional number of LCDs in column 1 is due to a correction for out-migration of the SDA population from the study area.

Columns 3, 7, 10, and 11 show the average numbers of individuals at risk annually during the study, allowing for those who died during the study. Columns 4 and 8 show the annual average lung cancer death rate (LCD) per 100,000 persons, and column 9 gives the differences between the non-SDAs and SDAs in those rates. Column 12 gives average LCD rates weighted to reflect the fact that there were three times as many women as men in the study, and that the female data attained statistical significance whereas the male did not—although the

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combined data were significant (Phillips *et al.*, 1980a, 1980b). A common LCD rate is assumed for both sexes in the calculation that follows. Also, it will be assumed that the entire LCD rate difference is due to passive smoking (see discussion on confounding factors in Appendix D).

Next, this calculation will be extrapolated to the entire U.S. nonsmoking population aged ≥ 35 yr. Column 13 gives the mean age of the individuals in the 5-yr age group, and column 14 gives the number of persons alive at that mean age per 100,000 born alive. Column 15 gives the total number of persons in the 5-yr age group (5 × column 14) per 100,000 born alive (whites only) from the 1974 U.S. Life Tables (USDHHS, 1975). Column 16 gives the age-specific LCD rates attributed to passive smoking, standardized to (i.e., weighted by) the age specific population distribution in 1974 for U.S. whites (column 12 times column 15).

Column 17 gives the average life expectancy corresponding to the mean age given in column 13, which is taken to represent that of the entire 5-yr age group. Column 18, the product of columns 16 and 17, gives the estimated age-specific age-standardized person-years of life lost due to lung cancer from passive smoking.

The sum of the values of column 18 gives an estimated 3932 person-yr of life lost due to passive smoking per 100,000 persons alive at age 35 in the U.S. population in 1979. 3932 person-yr, when divided by the 94,724 persons (USDHHS, 1975) at risk at age 40 (LCDs were not observed at earlier ages in the SDA study; however, they are observed in the general nonsmoking U.S. population at age 35) (USSG, 1979) yields 15 days, the mean number of days of life lost, and, multiplying by the peak-to-mean exposure ratio, 148 days for the maximum number of days lost (where the risks of the non-white population are taken to be the same as for the white population.)

Column 19 is column 16 times 62.424 million divided by the sum of column 15. The sum of column 19 gives an estimated age-standardized mortality total of 4,665 LCDs per year in U.S. nonsmokers from passive smoking (where there were 93,636,000 persons aged ≥ 35 yr

Table C1. Age-standardized estimation of lung cancer deaths from passive smoking.

5 yr. Age Group	SDA Never Smokers: 1. Total LCDs (17 yr period)	SDA Never Smokers: 2. Person yr at Risk	SDA Never Smokers: 3. Average Annual No. of Persons	4. LCDs per 100,000 Person Years	Non-SDA Never Smokers: 5. Total LCDs (12.58 yr period)	Non-SDA Never Smokers: 6. Person yrs. at Risk	Non-SDA Never Smokers: 7. Average Annual No. of Persons at Risk	8. LCDs per 100,000 Person Yrs
Females								
35-39	0	3791	223.0	0	0	5766	458.3	0
40-44	0	11494	676.1	0	1	16466	1308.3	6.0731
45-49	0	18757.5	1103.4	0	2	38319	3046.9	5.2193
50-54	1.119	24808.5	1459.3	4.5106	4	61630	4899.0	6.4909
55-59	1.000	24702	1453.1	4.0483	8	71289	5666.9	11.222
60-64	1.101	24051.5	1414.8	4.5777	7	65054	5171.2	10.760
65-69	1.148	23326.5	1372.1	4.9214	4	55614	4420.8	7.1924
70-74	0	21809	1282.9	0	9	44248	3517.3	20.340
75-79	1.000	18822	1107.2	5.3219	10	29250	2325.1	34.188
80-84	7.775	13435.5	790.3	57.869	6	15301	1216.3	39.213
85+	2.258	10017.5	589.5	22.541	10	7891	627.3	126.73
Total	15.401	195,015	11,472	103.7899	61	410,828	32,657	267.4247
Males								
35-39	0	1926.5	113.0	0	0	1581	119.3	0
40-44	0	5732.5	337.2	0	0	3479	276.6	0
45-49	0	9177	539.8	0	0	9662	768.0	0
50-54	0	11480	675.3	0	1	19313	1535.2	5.1776
55-59	1.119	10359.5	609.4	10.8017	2	23848	1895.6	8.3865
60-64	1.000	8763.5	515.5	11.440	4	19535	1552.9	20.4761
65-69	3.401	7386.5	434.5	46.0435	8	14105	1121.2	56.7173
70-74	1.115	6360.5	374.1	17.5301	0	9786	777.9	0
75-79	0	5278.5	310.5	0	2	6541	520.0	30.5764
80-84	1.143	3957.0	232.8	28.8855	4	3517	279.6	113.733
85+	2.235	3160.0	185.9	70.7278	2	1671	132.8	119.669
Total	10.013	73581.5	4328.0	185.4266	23	113,038	8979.1	354.7564

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Table C1. (Continued).

	Females		Male/Female					
5 yr Age Group	9. Annual LCDs per 100,000 (Non-SDA)-(SDA)	10. Average Age-Specific No. of SDA & Non SDA at Risk	11. Average Age-Specific No. of SDA & Non SDA at Risk	12. Annual Weighted Mean LCD per 100,000 (unisex)	13. Mean age of 5 yr Group	14. Mean No. of Persons At Risk at each yr of 5 yr Group	15. Mean No. of Persons At Risk in Entire 5 yr Age Group	16. Age Specific Age Stand (1974 U.S. White Population) LCDs
35-39	0	681	913	0	37.5	95,201	476,005	0
40-44	6.0731	1985	2599	4.64	42.5	94,122	470,610	21.84
45-49	5.2193	4149	5457	4.50	47.5	92,339	461,645	20.77
50-54	1.9803	6358	8569	2.81	52.5	89,590	447,950	12.59
55-59	7.1737	7120	9625	4.67	57.5	85,477	427,385	19.96
60-64	6.1823	6586	8654	6.87	62.5	79,396	396,980	27.27
65-69	2.2710	5793	7349	4.05	67.5	71,177	355,885	14.41
70-74	20.340	4800	5952	13.0	72.5	60,455	302,275	39.30
75-79	28.875	3432	4263	29.2	77.5	46,689	233,445	68.17
80-84	−18.656	2006	2518	2.35	82.5	31,209	156,045	3.67
85+	104.189	1217	1536	92.6	87.5	11,913	59,565	55.16
Total	163.6477	44,127	57,435	164.69	(1974 Census (whites per 100,000 at Birth)		3,787,790	203.14

5 yr. Age	Males	
35-39	0	232
40-44	0	614
45-49	0	1308
50-54	5.1779	2211
55-59	−2.4152	2505
60-64	9.0651	2068
65-69	10.6740	1556
70-74	−17.5301	1152
75-79	30.5764	831
80-84	84.8475	512
85+	48.9612	319
Total	169.3568	13,308

Table C1. (Continued).

5 Yr. Age Group	17. Average life Expectancy for the 5-year Age Group	18. Person years of life lost due to LCDs from passive smoking	19. LCDs per year in age group in entire 1979 U.S. nonsmoking population aged ≥ 35 yr
35-39	–	0	0
40-44	33.1	723	360
45-49	28.7	596	343
50-54	24.6	310	207
55-59	20.8	415	329
60-64	17.2	469	449
65-69	14.0	202	237
70-74	11.1	436	647
75-79	8.6	586	1123
80-84	6.6	24	61
85+	3.1	171	909
	17 ± 9	3932	4665

in 1979, and two-thirds or 62,424,000 of these were nonsmokers).

Examining column 19, shows that of those individuals assumed to contract lung cancer from passive smoking, approximately 1½% do so at each year of age from 40 to 69, and over age 70, approximately 3% do so each year. Of those who actually contract fatal lung cancer from passive smoking, the mean life expectancy lost is about 17 ±9 yr, and about 8% lose as much as 33 yr.

Appendix D: Discussion of Confounding Factors

The IARC criteria for causality and human cancer specify that possible sources of bias and confounding error should be considered (IARC, 1979). What factors other than passive smoking could account for a lung cancer difference between two cohorts?

The most obvious one is misclassification. Some of the individuals classified as nonsmokers could have

been smokers or exsmokers, giving rise to a spurious effect. Workplace or residential exposure to lung carcinogens or dietary differences between the cohorts might also give rise to spurious differences. However, this is not likely to be an effect constant over 14 positive studies in six different countries, all of which report about a doubling of risk when the exposure variable is spouses' smoking.

Arsenic, asbestos, beryllium, chloroethers, chromium, coke oven emissions, nickel, radon, and vinyl chloride, as well as tobacco smoke, have been implicated in the etiology of lung cancer (Ives, 1983; Selikoff, 1981). Possible differences due to industrial exposures should be expected primarily in blue-collar workers. Phillips *et al.* (1980a, 1980b) have stated that the SDA/non-SDA subgroups were demographically and educationally similar, suggesting similar occupational distributions, although there is no information on this point. There is no reason to believe that domestic radon levels, which are a property of the soil, would be any different in SDA homes than non-SDA homes. Finally, it should be considered that co-exposures to other lung carcinogens (e.g., radon) may increase the effect of passive smoking (Bergman and Axelson, 1983).

It is also possible that dietary differences between the two groups might have contributed to the SDA/non-SDA lung cancer difference. For example, 54% of SDAs follow a lacto-ovarian diet and 41% rarely use caffeine beverages. However, Hirayama (1981a, 1981b, 1983a, 1983b) observed a dose-response relationship between exposure to passive smoking and lung cancer even in those with an apparently cancer-inhibiting diet. Also, SDA/non-SDA cancer differences are not significant for other smoking-related cancer sites; this runs counter to a protective effect of diet as a confounding factor. Finally, Hirayama (1983a) observed that the magnitude of this effect varied from a mortality ratio of 1 for passive smoking women who did not follow a protective diet to 0.82 for women who use green-yellow vegetables only occasionally, to 0.72 for women who ate them daily. Thus the magnitude of the effect does not appear to be sufficient to account for the observed SDA/non-SDA lung cancer difference. Moreover, if 40% of the SDAs work for church-run organizations, 60% do not; these 60% surely must be subject to some passive smoking in the workplace, at least partially offsetting the effects of potential dietary or occupational differences with the non-SDAs.

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NONSMOKER LUNG CANCER RISKS FROM TOBACCO SMOKE EXPOSURE: AN EVALUATION OF REPACE AND LOWREY'S PHENOMENOLOGICAL MODEL

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Contents:

INTRODUCTION

Nonsmokers may be exposed to measurable amounts of tobacco smoke in indoor environments such as offices; public areas such as shopping centers, bars and restaurants; and private residences, particularly if the ventilation is poor. This passive exposure to environmental tobacco smoke (ETS) is of concern because several epidemiological studies have indicated that ETS exposure may increase the risk of lung cancer (1,2). The magnitude of a possible excess lung cancer risk for nonsmokers from ETS exposure is therefore of interest.

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Repace and Lowrey (3) develop a "phenomenological model" which estimates an annual excess risk from ETS exposure of 7.4 lung cancer deaths (LCD)/100,000 nonsmokers 35 years of age and over. The risk calculation is limited to individuals 35 years of age and over because only 0.26% of lung cancer deaths in 1980 occurred among individuals less than 35 years of age (4). This excess risk, applied to an estimated U.S. population of 62.4 million nonsmokers, 35 years of age and over, predicts 4,655 nonsmoker lung cancer deaths from ETS exposure. The category "nonsmoker" includes both ex-smokers and life-long never smokers.

Repace and Lowrey's phenomenological estimate of the lung cancer risk from ETS exposure has been widely accepted in the U.S. and Canada (5). Yet, the estimate is based on several unrealistic assumptions and on unstable data that warrant closer examination. It is the purpose of this review to examine several problems with the phenomenological model and to evaluate the reliability of the lung cancer risk estimates derived from it.

THE PHENOMENOLOGICAL MODEL

Repace and Lowrey's phenomenological model extrapolates from the observed (hence phenomenological) results of a study on a special group of never smokers to the entire U.S. population of nonsmokers. The calculations use lung cancer incidence data from a cohort study by Phillips et al (6,7) of California Seventh Day Adventist (SDA) never smokers and a second cohort of California never smokers. The SDA cohort of never smokers were followed prospectively from 1960 until mid-1972 and the comparison never smoker cohort, from the American Cancer Society (ACS) 25-state study, was followed from 1960 to the end of 1976.

The study by Phillips et al does not examine the association between ETS exposure and lung cancer, nor is any information obtained on ETS exposure. However, the SDA group was probably less exposed to ETS than the nonSDA group because less than two percent of the SDAs were self-reported smokers as a result of the church proscription against smoking. Consequently, SDA never smokers are not likely to be exposed to ETS in church operated businesses, in their own homes, or in the homes of other church members.

Table I gives, for both SDA and nonSDA never smokers, the observed number of lung cancer deaths and the lung cancer death rate per 100,000 person-years for each 5-year age group starting from age 35. The age standardized relative risk of lung cancer for the SDA men and women compared to the nonSDA men and women is 1.73 and 2.54, respectively.

Repace and Lowrey assume that *all* of the difference in the lung cancer risk between SDA and nonSDA never smokers is caused by a difference in exposure to ETS. They estimate the lung cancer risk from ETS exposure in the following manner. First, the age-specific lung cancer risks for SDA never smokers are subtracted from the comparable risks for nonSDA never smokers. For example, the lung cancer death rate for nonSDA never smoking women 85 years of age and over is 126.73 per 100,000 (Table I, column 5), while the rate for the comparable group of SDA women is 22.54 (Table I, column 3). The difference, 104.19 LCD/100,000, is attributed entirely to ETS exposure. Second, the age-specific differences in risk for men and women are weighted in order to derive a single age-specific risk estimate. For example, the difference between SDA and nonSDA men over 85 is 48.96 LCD/100,000. The combined average for the over 85 age group, weighted by the number of person-years of observation for

TABLE I

Number of lung cancer deaths and the lung cancer death rate per 100,000 person-years (LCD/100,000) for Seventh Day Adventist (SDA) and nonSDA never smokers (1)

MEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	0	0
45-49	0	0	0	0
50-54	0	0	1	5.18
55-59	1	10.80	2	8.39
60-64	1	11.44	4	20.48
65-69	4	46.04	8	56.72
70-74	1	17.53	0	0
75-79	0	0	2	30.58
80-84	1	28.89	4	113.73
85+	2	70.73	2	119.69

WOMEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	1	6.07
45-49	0	0	2	5.22
50-54	1	4.51	4	6.49
55-59	1	4.05	8	11.22
60-64	1	4.58	7	10.76
65-69	1	4.92	4	7.19
70-74	0	0	9	20.34
75-79	1	5.32	10	34.19
80-84	8	57.87	6	39.21
85+	2	22.54	10	126.73

*The actual number of observed deaths is estimated from Repace and Lowrey's figures, which were adjusted for the effect of outmigration.

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men and women, is 92.6 LCD/100,000. Third, the average risk estimates for both sexes combined are applied to the estimated population distribution of the 62.4 million nonsmokers 35 years of age and over in the U.S. in 1980, which is assumed to be the same as the age distribution of the entire U.S. population in 1974. For example, the excess lung cancer risk from ETS exposure of 92.6 LCD/100,000 men and women 85 years of age and over, combined, is applied to the estimated 981,164 nonsmokers over 85 in the U.S. in 1980. This predicts 909 excess lung cancer deaths in this age group [(92.6 x 981,164)/100,000]. Fourth, the excess lung cancer deaths for all age groups over 35 are summed. This adds up to 4,655 excess lung cancer deaths among the 62.4 million nonsmokers, which gives an annual risk from ETS exposure of 7.4 LCD/100,000 nonsmokers 35 years of age and over.

PROBLEMS WITH THE PHENOMENOLOGICAL MODEL

There are three problems with Repace and Lowrey's phenomenological model.

1. The lung cancer risk estimates derived from the SDA study are based on very few observed deaths and are unstable.
2. The apparent differences in lung cancer mortality between SDA and nonSDA never smokers may be due to a variety of factors other than ETS exposure.
3. A number of assumptions and calculations are made that are clearly incorrect.

1. Stability of the Model

The reliability of Repace and Lowrey's phenomenological model is strongly dependent upon the accuracy of the

age-specific lung cancer death rates calculated for the SDA and nonSDA never smokers. However, the SDA lung cancer death rates, in particular, are not likely to be accurate because they are based on a small number of observed lung cancer deaths.

There were only 10 lung cancer deaths among the SDA men (the difference in risk between SDA and nonSDA men is not, in fact, statistically significant) and 15 deaths among the SDA women (6). The age-specific risks for 9 out of the 22 age groups are based on only one lung cancer death and there were no lung cancer deaths in an additional nine of the age groups. Consequently, the age-specific rates for SDA men and women varied widely, as shown in column 3 of Table I. For example, the lung cancer death rate for SDA women over 85 was less than half the rate for the preceding age group. This decline of lung cancer risk with age must be due to random or other errors, because lung cancer death rates invariably increase with age (8,9).

The small number of lung cancer deaths observed for the SDA cohort may be partly attributable to a lack of histopathological verification and incomplete follow-up. These two problems did not occur in the nonSDA cohort, which may partly explain the large difference in the lung cancer rates between the two cohorts. The SDA cohort was also relatively small so that few lung cancer deaths would be expected. Random fluctuations in the number of observed lung cancer deaths would result in large differences in the age-specific lung cancer death rates. Therefore, these rates are very unstable.

The phenomenological model is very sensitive to errors in the estimated lung cancer death rates for SDA never smokers. For example, adding one lung cancer death to the 70-74 year age

group for SDA women results in 183 fewer estimated deaths per year in the U.S., according to the method used by Repace and Lowrey (3). A second example concerns the over 85 age group. As noted above, the observed lung cancer death rate of 22.5 LCD/100,000 SDA women 85 years of age and older is not likely to be correct, and is probably a large underestimate of the true rate. This underestimate is responsible for a significant proportion of all lung cancer deaths attributed to ETS exposure. 909, or 19.5%, of the estimated 4,655 excess lung cancer deaths in the U.S. among all nonsmokers 35 years of age and over occur among individuals over 85 years of age. The majority of these deaths are attributable to the estimated risk for women over 85 because of the large difference of 104.2 LCD/100,000 between the rate of 22.5 LCD/100,000 SDA women and 126.7 LCD/100,000 nonSDA women in this age group. An increase in the lung cancer death rate for SDA women over 85 years of age to a rate greater than that observed for women between 80-84 years of age (57.9 LCD/100,000) would decrease the difference between the SDA and nonSDA cohorts and consequently decrease the predicted risk and number of deaths attributable to ETS exposure.

For several age groups, the phenomenological model predicts more lung cancer deaths among never smokers as a result of exposure to ETS alone than a reasonable estimate of the total number of lung cancer deaths from all causes, as shown in Table II for men and Table III for women. The number of expected lung cancer deaths is obtained by multiplying the age-specific lung cancer death rates from ETS exposure alone (column 3) or from all causes (column 5) by an estimate of the number of never smokers in each age and sex category (column 2). The latter is obtained by combining the 1979/1980 Health Interview Survey

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TABLE II

Comparison of the estimated number of lung cancer deaths (LCD) in 1980 among male never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Never smoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	1,983,771	0	0	0	0
40-44	1,713,801	0	0	7.6667	131.3898
45-49	1,238,080	0	0	3.0333	37.5890
50-54	1,328,762	5.1778	68.80		
55-59	1,127,890	-2.4152	-27.24	10.1333	114.2884
60-64	1,162,535	9.0484	105.38	17.2667	200.7314
65-69	1,094,361	10.6740	116.81	27.4333	300.2193
70-74	886,253	-17.5301	-155.36	77.9000	690.3911
75-79	722,388	30.5764	220.88	44.2667	319.7818
80-84	382,727	84.8475	324.73	68.8667	263.5715
85+	303,790	48.9612	148.74	94.8000	287.9929
			Total 802.74		Total 2,447.39

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

TABLE III

Comparison of the estimated number of lung cancer deaths (LCD) among female never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Neversmoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	3,388,446	0	0	0	0
40-44	2,870,313	6.0731	174.31	2.3333	66.97
45-49	2,887,520	5.2183	150.71	3.6000	103.95
50-54	3,242,330	1.9803	64.21	5.3000	171.84
55-59	3,147,137	7.1737	225.77	7.0667	222.40
60-64	2,982,713	6.1823	184.40	13.6000	405.65
65-69	2,979,828	2.2710	67.67	16.1667	481.74
70-74	2,616,364	20.3400	532.17	20.8333	545.08
75-79	2,157,707	28.8750	623.04	34.7000	748.72
80-84	1,528,857	-18.6560	-285.22	45.8000	700.22
85+	1,026,830	104.1090	1,068.92	52.4667	538.80
			Total 2807.01		Total 3,985.37

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

(HIS) estimates of the proportion and age and sex distribution of never smokers with the U.S. Census estimate of the population 35 years of age and over in 1980 (10,11). The estimated number of lung cancer deaths from ETS exposure alone is given in column 4 of each table. The all causes estimate uses the lung cancer death rates observed for never smokers in the ACS 25-state study (8). The estimated number of lung cancer deaths from all causes is given in column 6 of each table.

The phenomenological model estimates fewer male never smoker lung cancer deaths from ETS exposure than the estimated number of deaths from all causes. However, for women, the model estimates almost the same number of lung cancer deaths from ETS exposure than from all causes for the age group 70-74 and *more* deaths from ETS exposure than from all causes for the age groups 40-44, 45-49, 55-59 and 85+. For example, the estimate of 1,069 female deaths attributable to ETS exposure in the 85+ group is almost twice the estimate of 539 deaths from all causes. The fact that the phenomenological model predicts, for several age groups, more lung cancer deaths from ETS exposure alone than from all causes indicates that the death rates used in the model are unreliable indicators of the real risk associated with ETS exposure.

<u>2. Other Causes for the Difference in Risk Between SDA and NonSDA Nonsmokers</u>

Repace and Lowrey's phenomenological model assumes that all of the difference in lung cancer incidence between the SDA and nonSDA never smokers is caused by ETS exposure. This assumption does not allow for other possible confounding factors, such as

differences between the SDA and nonSDA cohorts in diet or exposure to occupational carcinogens.

The possibility of confounding by occupation, though possible, cannot be assessed. Phillips et al (6,7) did not determine the occupational distribution of SDA and nonSDA never smokers because occupation was coded differently for the two groups. Occupation would affect the estimated risks if a higher proportion of the nonSDA versus SDA never smokers were blue-collar workers exposed to carcinogens at work.

Confounding by diet is probable. A low rate of consumption of vegetables or foods containing retinoids has been linked to an increased lung cancer risk (12-15). The SDAs are known to follow a lacto-ovo vegetarian diet and this may reduce their risk for many types of cancer, both through a decreased intake of fats and an increased consumption of vegetables, eggs, and milk high in retinoids or vitamin A. Therefore, the low lung cancer incidence among the SDA never smokers may be due to dietary factors such as an above average consumption of retinoids. A possible dietary cause for the difference in the lung cancer risk between the SDA and nonSDA never smokers is supported by the lower risks for colon-rectal and breast cancer observed for the SDA group. Several studies have found that diet may be a risk factor for colon-rectal (16) and breast cancer (17). There was a statistically significant decrease in the relative risk (RR) of breast cancer (RR = 0.81) and colon-rectal cancer (RR = 0.56) for SDA women never smokers compared to the nonSDA women never smokers (6). The relative risk of colon-rectal cancer for SDA men was also below 1.0 but was not statistically significant.

3. Other Errors

There are three instances where Repace and Lowrey make inappropriate assumptions.

1. Repace and Lowrey incorrectly assume that nonsmokers have the same sex and age distribution as the entire U.S. white population. A comparison between the 1979/1980 HIS data and U.S. Census data (10) shows that the age distribution of the U.S. nonsmoking population is skewed towards the older age classes, as shown in Table IV. For example, 25.38% of male nonsmokers 35 years of age and over are between the ages of 35 and 44 compared to 28.76% of all U.S. males 35 years of age and over and 10.5% of nonsmoking males are 75 years of age or over compared to 8.1% of all U.S. males.
2. Repace and Lowrey combine both sexes, instead of calculating the expected number of deaths for each sex separately. The latter is required, as the age distribution of female never and nonsmokers is different from the comparable distributions for men, as shown in Table IV.
3. Repace and Lowrey estimate the excess lung cancer deaths from ETS exposure for nonsmokers (ex- and never smokers combined). This should not be done because the difference in lung cancer death rates between the SDA and nonSDA group is for never smokers only. The excess risk for ex-smokers from exposure to ETS may differ from the risk for never smokers, either because of their previous smoking habit or because ever smokers are more likely than never smokers to be exposed to carcinogens at work (18).

IS THERE INDEPENDENT SUPPORT FOR THE PHENOMENOLOGICAL MODEL?

The phenomenological model, based on only 25 lung cancer deaths among never smoking men and women SDAs combined, provides

TABLE IV

1979/1980 HIS estimates of the age distributions of never and nonsmokers and the U.S. Census estimate for adults 35 years of age and over

MEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	31.00	25.38	28.76
45-54	21.47	23.01	24.80
55-64	19.15	22.40	23.00
65-74	16.56	18.66	15.34
75-84	9.24	8.44	6.54
85+	2.54	2.06	1.56

WOMEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	21.70	23.09	25.38
45-54	21.25	21.67	22.67
55-64	21.25	21.92	22.34
65-74	19.40	19.21	17.10
75-84	12.78	11.14	9.46
85+	3.56	2.92	3.05

an unstable estimate of the lung cancer risk for nonsmokers as a result of ETS exposure. Repace and Lowrey, though not directly addressing this problem, use corroborative evidence to defend the estimated annual risk of 7.4 LCD/100,000. They argue that their findings are supported by 1) the results of a linear extrapolation model, after adjusting for the nonsmoker's retained ETS dose and 2) a sensitivity analysis of the ACS study on ETS exposure and lung cancer (8).

1. Linear Extrapolation Model

Nonsmoker lung cancer risks from ETS exposure can be calculated by using a linear extrapolation model. This method

estimates the risk for nonsmokers by dividing the lung cancer risk for current smokers by the ratio between the smoker's and nonsmoker's average exposure. The linear model requires estimates of several parameters such as the number of nonsmokers and current smokers in the U.S. and their average daily exposure to ETS. The linear extrapolation model also requires three assumptions, 1) that it is valid to derive the lung cancer risk for nonsmokers exposed to ambient ETS from the observed risk for smokers exposed to directly inhaled tobacco smoke, 2) that there is a linear relationship between risk and each unit of exposure, and 3) that no threshold exists at very low exposures where the risk falls to zero.

Repace and Lowrey (3) pioneered the development of the linear model for estimating nonsmoker lung cancer risks from ETS exposure. Their linear extrapolation calculation estimates a lung cancer risk for nonsmokers of 0.83 LCD/100,000 from ETS exposure. This is significantly lower than the phenomenological model's estimate of 7.4 LCD/100,000. Repace and Lowrey argue that the difference between the two risk estimates can be explained by the difference between the nonsmoker's inhaled exposure and the equilibrium ETS dose.

The inhaled exposure is based on the amount of ETS inhaled, whereas the equilibrium dose calculates the steady-state burden of particulate ETS in the lungs from the inhaled exposure. The following equation calculates the equilibrium dose (3):

$$\text{Equilibrium dose} = D_n \delta \tau,$$

where D_n equals the inhaled exposure in milligrams (mg); δ equals the deposition fraction for tobacco smoke particulates in the lungs; and τ equals the mean life for pulmonary clearance,

which is assumed to be 101 days. The deposition fraction for nonsmokers has been empirically estimated to be approximately 11% (19). Repace and Lowrey estimate that the equilibrium dose for the average nonsmoker inhaling 1.43 mg/day is 16 mg/day (1.43 mg x .11 x 101), which is 1/34th of their estimate of the average smoker's daily inhaled exposure of 544 mg. Repace and Lowrey's estimate of the lung cancer risk for current smokers is 315.6 LCD/100,000. Therefore, the linear model predicts a lung cancer risk for never smokers of 9.28 LCD/100,000 (315.6/34). Accordingly, the risk estimates derived from the linear and phenomenological models are approximately the same, with the phenomenological model providing the lower risk estimate.

In fact, Repace and Lowrey's adjustment of the linear model is based on an incorrect comparison between two completely different estimates of exposure. The *exposure* of smokers is compared to the *equilibrium dose* of nonsmokers. Obviously, the correct comparison is either between the smoker and nonsmoker's inhaled exposure or between the smoker and nonsmoker's equilibrium dose. An estimate of the lung cancer risk for nonsmokers, using the linear model and the equilibrium dose, can be determined using an estimate of the deposition fraction for smokers.

The deposition fraction for smokers has been empirically estimated to be between 70% and 96% (19-22). We will assume an average retention rate of 80% for smokers. The equilibrium dose for smokers, using Repace and Lowrey's estimate of the inhaled exposure for smokers of 544 mg, is 43,955 mg (544 x 0.80 x 101). Therefore, nonsmokers have only 1/2,747th of the smoker's equilibrium dose (43,955/16) and, consequently, only 1/2,747th of the smoker's lung cancer rate, or 0.11 LCD/100,000

(315.6/2,747). Instead of supporting the phenomenological estimate, the use of the equilibrium dose in the linear model significantly decreases the likelihood that the phenomenological model provides a reliable estimate of the average risk for nonsmokers from ETS exposure.

2. Sensitivity Analysis

Repace and Lowrey (3) conduct a sensitivity analysis to explain the difference in the results of two cohort studies, one in Japan and one in the U.S., of female nonsmokers married to smokers. The sensitivity analysis uses an estimate of risk per 1 mg of exposure to tobacco smoke particulate that is based on the phenomenological model. Garfinkel's (8) analysis of the ACS data for 176,731 American women followed from 1960 until 1971 finds a statistically nonsignificant increased relative risk of 1.20 for never smoking women married to smokers. Conversely, Hirayama's (23) study of 91,540 Japanese women followed from 1966 to 1981 finds a statistically significant increased relative risk of 1.78, which is closer to the relative risk of 1.73 for men and 2.54 for women on which the phenomenological model is based.

Repace and Lowrey suggest that the ACS relative risk is unrealistically low and actually results from confounding with workplace exposure, which they estimate to contribute four times as much exposure to ETS as the home environment. The ACS study does not include workplace exposure as a factor in deciding exposure status. Nonsmoking women married to smokers are defined as exposed, whereas nonsmoking women married to nonsmokers are defined as unexposed. Repace and Lowrey estimate that 38 percent

of the original unexposed and exposed ACS women worked outside the home and were therefore exposed to ETS at work.

Repace and Lowrey's sensitivity analysis recalculates the ACS results using an estimate of the lung cancer risk per 1 mg of ETS exposure and an estimate of the amount of home and workplace exposure recieved by the original ACS exposed and unexposed cohorts. The lung cancer risk per 1 mg of exposure is estimated by combining the phenomenological model's estimated risk of 7.4 LCD/100,000 with an estimated average daily exposure to 1.43 mg of ETS. This estimates a risk of 5 LCD/100,000 per mg of exposure. The excess lung cancer risk from ETS exposure for each of four exposure categories - women not exposed at home or at work, women exposed at work only, women exposed at home only, and women exposed at home and at work - is determined by multiplying the estimated exposure by the risk of 5 LCD/100,000 per mg of exposure. For example, Repace and Lowrey estimate that employed women are exposed to 1.82 mg/day and women who live with a smoker are exposed to 0.45 mg/day. Therefore, women who both work and live with a smoker are exposed to 2.27 mg/day for an excess risk of 11.35 LCD/100,000 (2.27 x 5). The excess risk from ETS exposure is added to the background lung cancer risk in the absence of any exposure in order to construct an expected death rate for each of the four exposure categories. The lung cancer death rate of 8.7 per 100,000 person-years found in the Japanese cohort study for nonsmoking women married to nonsmoking men is used as the base lung cancer rate in the absence of either work or home exposure to ETS.

The relative risk of 1.19 for women who live with a smoker versus those who do not, determined after the adjustment for work exposure and the use of the phenomenological model's

estimate of risk, is only marginally different from the original "unadjusted" risk of 1.20. According to Repace and Lowrey, this indicates that the estimated risk from the phenomenological model is a good estimator of the true risk in this cohort study.

Problems with the sensitivity analysis

Repace and Lowrey's sensitivity analysis is dependent upon 1) the applicability of the background lung cancer death rate in the absence of smoking and 2) the relative importance of exposure at work versus exposure at home.

1. The background risk

The use of the risk of 8.7 LCD/100,000 Japanese women nonsmokers as an estimate of the background risk in the Garfinkel study is inappropriate. Repace and Lowrey note that the risk of 8.7/100,000 is an 'age-adjusted' risk, *but it is adjusted to the age distribution of the husbands of the Japanese female nonsmokers and not to the ACS women at risk.* It is unlikely that the age distribution of Japanese male nonsmokers is the same as the age distribution of American female nonsmokers.

The age distribution of the entire ACS population of nonsmoking women is available and can be compared against the age distribution used in Hirayama's study. Both distributions are given in Table V. If we assume that the age distribution of nonsmoking women married to nonsmokers in the ACS study is similar to the age distribution of all nonsmoking ACS women, it is possible to apply the age-specific lung cancer death rates from the Japanese study to the ACS population distribution, as shown in Table VI. The background lung cancer death rate is

TABLE V

Age distribution of 375,381 nonsmoking women at the start of the ACS study and the nonsmoking husbands of 21,895 nonsmoking women at the start of the Hirayama study

AGE	ACS (24)	Hirayama (1)
under 49*	0.3374	0.2845
50-59	0.3278	0.3558
60-69	0.2201	0.3252
70+	0.1147	0.0345

* ACS population starts at 30 years of age and the Hirayama population of husbands at 40 years of age.

TABLE VI

Estimated lung cancer death rate (LCD/100,000) for nonsmoking women from the ACS study (8) after using the husband-age-specific risks for nonsmoking women from Hirayama (1)

AGE	Hirayama: LCD/100,000*	Age Distribution of ACS nonsmokers	Expected LCD's
under 49	4.01	0.3374	1.35
50-59	8.02	0.3278	2.63
60-69	15.80	0.2201	3.48
70+	41.39	0.1147	4.75
		Total LCD/100,000	12.21

* Age-specific LCD/100,000 person years, adjusted for the husband's age (1).

subsequently increased from 8.7 to 12.21 LCD/100,000. This is similar to the rate for all nonsmoking ACS women of approximately 13/100,000, which indicates that there is no increase in risk in the ACS study from ETS exposure.

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The background risk of 12.21 LCD/100,000 can be used in the sensitivity model, keeping in mind that the model is extremely insensitive to large differences in risk. For example, the use of the phenomenological estimate of the excess lung cancer risk from ETS exposure results in a 1% difference between the adjusted relative risk of 1.19 and the observed relative risk of 1.20. Decreasing the estimate of the excess risk 8.3-fold only increases the difference between the adjusted and observed relative risks by 17%. A change in the background risk from 8.7 LCD/100,000 to 12.21 LCD/100,000 increases the difference between the adjusted and observed relative risk from 1.0% to 4.6%, which is a significant change considering the insensitivity of the sensitivity analysis. This indicates that the estimate of risk from the phenomenological model is a poor indicator of the true risk in the ACS population.

The use of the background lung cancer rate from the Japanese study is also questionable. It assumes that none of the Japanese women worked. Accordingly, it is unnecessary to adjust their baseline lung cancer death rate for workplace exposure to ETS. In fact, between 31% and 34% of Japanese women worked in paid employment during the time period of the Hirayama study (25), and 15% of Japanese women smoked (26). Therefore, some workplace exposure must have occurred from exposure to the tobacco smoke of fellow male and female employees.

2 Adjustment for work exposure

The sensitivity analysis is dependent upon Repace and Lowrey's estimate, based on an exposure model, that workplace exposure accounts for 80.4% of the total daily average exposure to ETS, while home exposure accounts for only 19.6%. However, there is no independent supporting evidence for Repace and

Lowrey's estimate on the relative importance of workplace versus home exposure from interview data (27) or from epidemiological studies. None of the four epidemiological studies which specifically examine the effect of exposure of women to ETS at work finds a statistically significant increase in risk (15,28-30).

DISCUSSION AND CONCLUSIONS

Other than Repace and Lowrey's phenomenological model, two methods are available for estimating the lung cancer risk or number of lung cancer deaths among nonsmokers from ETS exposure. These methods consist of 1) a downward extrapolation from the risk for smokers and 2) the population attributable risk (PAR) equation (31).

The linear extrapolation model was developed by Repace and Lowrey (3) and has been further refined by Arundel et al (32). As shown above, Repace and Lowrey's linear model does not support the results of the phenomenological model. In addition, the risk estimate of 0.83 LCD/100,000 nonsmokers, determined by Repace and Lowrey from the linear model, is inaccurate. This is because their linear model overestimates the average nonsmoker's exposure to ETS and the average current smoker's lung cancer risk. For example, the latter is estimated by Repace and Lowrey after assuming that all lung cancer deaths among ever smokers (ex- and current combined) occur only among current smokers. This results in a significant overestimate of the lung cancer risk for current smokers and, subsequently, for never smokers.

The linear model developed by Arundel et al (32) estimates a lung cancer risk from ETS exposure for both sexes combined of 0.022 LCD/100,000. This estimate is based on the equilibrium

dose. However, the calculations by Arundel et al, as do those by Repace and Lowrey, rest on several assumptions that may not be tenable.

The large difference in the linear estimates by Repace and Lowrey and by Arundel et al illustrates the extensive uncertainty which accompanies the results of these types of models. Large errors in the risk estimates are possible in any type of model. Arundel et al provide a "sensitivity calculation" which indicates the effect of a 1% change in each parameter of the linear model on the final risk estimate. This is useful for determining the most important parameters in the model, but does not replace scientifically desirable confidence limits.

The PAR equation estimates the number of lung cancer deaths from ETS exposure using differences in risk observed in epidemiological studies. In this respect it is similar to the phenomenological model, but the number of lung cancer deaths from ETS exposure is calculated using only three parameters: the exposure rate in the population of interest, the relative risk of exposure, and an estimate of the number of nonsmokers in 1980 (obtainable from the 1979/1980 HIS). Therefore, the PAR equation appears to be a remarkably simple method for estimating the number of lung cancer deaths among nonsmokers from ETS exposure. However, neither the exposure rate nor the relative risk are known for the entire population of nonsmokers. The exposure rate could be estimated from HIS data on the employment status of nonsmokers and the proportion who live with a smoker. Unfortunately, the relative risk cannot be estimated because most of the epidemiological studies on this problem only calculate risks for a subset of all nonsmokers (married women) exposed to a subset of all possible exposures (spouse's smoke) (2,8,23,33-37).

The relative risk is particularly difficult to obtain because the PAR method requires an estimate of the relative risk for the *average* regularly exposed nonsmoker compared to the *average* unexposed nonsmoker. The relative risk must not be determined from a subset of the regularly exposed population of nonsmokers. Exposure should also be defined as cumulative exposure to all sources of ETS.

An accurate method for estimating the lung cancer risk and the number of lung cancer deaths among nonsmokers from ETS exposure is of considerable interest. Repace and Lowrey's phenomenological estimate of the lung cancer risk for nonsmokers from ETS exposure is unstable and inaccurate. The evidence presented by Repace and Lowrey to support the plausibility of their estimate is based on several errors and unrealistic assumptions. Without corroborating data from independent sources, little confidence can be placed in their results.

The results of the linear extrapolation model by Arundel et al and the results of the best available epidemiological studies further indicate that the phenomenological estimate is in error. Both predict an extremely small excess lung cancer risk from ETS exposure. Conversely, Repace and Lowrey argue that the 12 epidemiological studies on ETS exposure support the plausibility of a significant excess risk from ETS exposure. However, with one exception (for men exposed at work) (29), the observed risks are statistically significant only when the analysis of exposure is limited to a comparison between female never smokers who are currently married to smokers versus married to nonsmokers. Exposure may also occur at work or at home from other household members and from previous spouses. Therefore, epidemiological studies should examine cumulative exposures from all sources.

The best available epidemiological analyses, by Koo et al (28) in Hong Kong and Garfinkel et al (30) in the United States, examine exposure from all sources. Neither find a statistically significant increase in risk. Garfinkel et al (30) also correlate cumulative exposures from all sources over the previous five or twenty-five years against lung cancer incidence and find a negative correlation between an increase in exposure and lung cancer. These analyses of cumulative exposures indicate that an association between lung cancer among nonsmokers and the spouse's smoking habit may be caused by confounding, not by ETS exposure. Confounding could occur either from life-style factors and occupational exposures associated with active smoking or by unreported active smoking by self-reported nonsmokers (38).

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NEVER SMOKER LUNG CANCER RISKS FROM EXPOSURE TO PARTICULATE TOBACCO SMOKE

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The average particulate environmental tobacco smoke (ETS) exposure of never and current smokers and the average lung cancer mortality rate for current smokers is estimated from empirical data. These estimates are used in a linear downward extrapolation of the lung cancer risk/mg of particulate ETS exposure for current smokers to calculate the average lung cancer risk for never smokers and the number of never smoker lung cancer deaths (LCD) in the U.S. in 1980 from exposure to particulate ETS. The estimated average daily inhaled particulate ETS exposure for never smokers is 0.62 mg/day for men and 0.28 mg/day for women. The average never smoker is estimated to retain 11% of the inhaled exposure, for a daily retained exposure of 0.07 mg for men and 0.03 mg for women. Other estimates are: **a daily retained exposure for current smokers of 310 mg for men and 249 mg for women, a smoking-attributable lung cancer risk for current smokers in 1980 of 284 LCD/100,000 men and 121 LCD/100,000 women, and** an annual retained-exposure lung cancer risk for never smokers of 0.64 LCD/100,000 men and 0.015 LCD/100,000 women. These risks and exposures estimate 12 lung cancer deaths among never smokers from exposure to particulate ETS: 8 among the 11.96 million male never smokers and 4 among the 28.85 million female never smokers in the U.S. in 1980. Conversely, between 655 and 3,610 never smoker lung cancer deaths are estimated from methods based on the average lung cancer risk observed in epidemiological studies of exposure to ETS. Three possible reasons for the discrepancy between the exposure and risk-based estimates are discussed: the excess risks observed in epidemiological studies are due to bias, the relationship between exposure and risk is supralinear, or sidestream tobacco smoke is substantially more carcinogenic than an equivalent exposure to mainstream smoke.

Introduction

Never smokers can be passively exposed to tobacco smoke at work, at home, and in public areas such as shopping centers and restaurants, particularly if the ventilation is poor. Concern over the average never smoker's lung cancer risk from exposure to "environmental" tobacco smoke (ETS) has grown considerably since a 1981 study reported an association between lung cancer in nonsmokers and marriage to a smoker (Hirayama, 1981). Since then, other epidemiological studies of the association between lung cancer among nonsmokers and ETS exposure from living with a smoker have been conducted in Japan (Akiba *et al.*, 1986), Greece (Trichopoulos *et al.*, 1983), Hong Kong (Chan & Fung, 1982; Koo *et al.*, 1985), Sweden (Pershagen *et al.*, 1987), Great Britain (Gillis *et al.*, 1984; Lee *et al.*, 1986), and the U.S. (Garfinkel *et al.*, 1981; Correa *et al.*, 1983; Buffler *et al.*, 1984; Kabat & Wynder, 1984; Garfinkel *et al.*, 1985; Dalager *et al.*, 1986; Brownson *et al.*, 1987; and Humble *et al.*, 1987). The results of these studies have been used to estimate an average excess lung cancer risk for never smokers of 30% from ETS exposure (Blot & Fraumeni, 1986; NRC, 1986; Wald *et al.*, 1986; Wigle *et al.*, 1987). Alternatively, the risk can be estimated by downward extrapolation techniques based on the lung cancer risk for current smokers and the average exposure of current and never smokers. The former method is a risk-based estimate whereas the latter is an exposure-based estimate.

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Linear Extrapolation

This study uses linear downward extrapolation to estimate the lung cancer risk and the number of U.S. lung cancer deaths for male and female never smokers in 1980 from exposure to ETS. The final estimate of the number of ETS-attributable never smoker lung cancer deaths requires four preliminary estimates:

1. The number of never smokers at risk,
2. The average tobacco smoke exposure of never smokers,

3. The average tobacco smoke exposure of current smokers, and
4. The smoking-attributable lung cancer risk for current smokers.

The lung cancer risk for never smokers is estimated by dividing the lung cancer risk for active smokers by the ratio of the average tobacco smoke exposure of smokers and never smokers. The estimated lung cancer risk for never smokers is then used to predict the number of ETS-attributable never smoker lung cancer deaths in the U.S. in 1980. This is done by multiplying the estimated lung cancer risk for each sex by an estimate of the total U.S. population of never smokers of each sex ≥ 35 years of age. Appendix A lists the equations and parameters used in the linear extrapolation estimate.

Estimating the smoker/never smoker exposure ratio

The major difficulty with the extrapolation method is to determine the smoker/never smoker exposure ratio. Ideally, the exposure ratio is based on carcinogenically equivalent exposures, such that one unit of exposure for a never smoker has the same lung cancer risk as one unit of exposure for an active smoker. However, no carcinogenically equivalent measure of exposure exists because smokers and never smokers inhale different types of tobacco smoke. Smokers mostly inhale mainstream smoke produced at temperatures above 600°C and then drawn through the cigarette and filter, whereas the ETS inhaled by never smokers consists mostly of sidestream smoke formed between puffs at 350°C and, partly, of exhaled mainstream smoke. Due to the different combustion temperatures, the amount of specific carcinogens in mainstream and sidestream smoke differs. For example, measurements of two brands of modern filter cigarettes find that fresh sidestream smoke contains 42 times more N-nitrosodimethylamine and 1.5 times more benzo(a)pyrene, but 15% less catechol (a major cocarcinogen (Hecht *et al.*, 1981)) and 70% less N-nitrosonornicotine, by weight, than mainstream smoke (Adams *et al.*, 1985). The problem of the relative carcinogenicity of mainstream and sidestream smoke is exacerbated by the possibility of substantial differences in the composition of their gaseous and particulate phases; however, this has not been studied adequately. Overall, the relative carcinogenicity per unit weight of mainstream and sidestream smoke is not known, though there is some evidence to indicate that particulate sidestream smoke is more carcinogenic than mainstream smoke. An animal study cited by Wynder and Hoffman (1967) finds more skin cancers among shaved mice painted with particulate sidestream versus mainstream condensates. A series of four Ames mutagenicity assays finds particulate sidestream smoke to be over ten times more mutagenic than an equivalent amount, by weight, of mainstream smoke in one test series, though there is little difference in the other three tests (Lofroth & Lazaridis, 1986).

In the absence of a measure of the carcinogenicity of mainstream and sidestream smoke, this study uses the current and never smoker's retained exposure to particulate ETS to estimate the smoker/never smoker exposure ratio. The exposure estimate adjusts for the dilution of sidestream smoke by ambient air. As a first approximation, the carcinogenicity of mainstream and sidestream particles is assumed to be equal (the effect of assuming a greater carcinogenicity for sidestream smoke is discussed later). Exposure to the gas phase of mainstream and sidestream smoke is not included because exposure to the gas phase, without concurrent exposure to tobacco smoke particulates, has not been found to cause lung cancer (Hoffmann *et al.*, 1978; SG, 1982). However, it is possible that future research may establish a significant carcinogenic role for the gas phase.

The smoker/never smoker exposure ratio is also based on the retained exposure (the amount of particulate by weight deposited in the lungs) instead of the inhaled exposure. A significant proportion of the latter is immediately exhaled and, consequently, has no effect on carcinogenesis. Hiller *et al.* (1982) experimentally determine in 11% particulate retention rate for never smokers exposed to sidestream smoke. Similar results have been found for other particulates in the size range of sidestream smoke (Davies *et al.*, 1972; Heyder, 1982). Conversely, the average active smoker retains between 47% and 96% of inhaled mainstream smoke, with most estimates falling above 70% (Dalhamm, 1968; Hoegg, 1972; Corn, 1974; First, 1984). The higher deposition rate for active smokers is thought to result either from deeper inhalation (Muir, 1974), hygroscopic growth and coagulation (Hiller *et al.*, 1982), or from electrical charges in mainstream smoke (Stober, 1984).

ETS exposure and cotinine. Tobacco smoke exposure can also be determined from blood, urine or saliva levels of cotinine — a nicotine metabolite. Cotinine appears, at first, to be a more accurate measure of exposure than retained particles. The latter can only be indirectly estimated for never smokers from exposure to all respirable particles, which include dust, pollen, and other aerosols. In contrast, cotinine is an accurate and specific indicator of tobacco smoke exposure because it is the only important source of exposure to nicotine. Cotinine also measures dose (the amount of a tobacco constituent metabolized by the body), whereas an estimate of retained particles only measures exposure. Unfortunately, though several studies show that cotinine levels in body fluids can accurately differentiate between never smokers with high, moderate and low ETS exposure (Jarvis *et al.*, 1984; 1985) or between nonsmokers and current smokers (Wald *et al.*, 1984), cotinine levels in never and current smokers are not directly comparable. This is

Table 1. Estimated number of never, ex-, and current smokers ≥ age 35 in 1980 in the U.S.*

	Men		Women		
Smoking Status	Number	Percent	Number	Percent	Total
Never	11,960,000	27.03	28,846,000	55.66	40,806,000
Ex-	15,314,000	34.62	7,774,000	15.00	23,088,000
Current	16,965,000	38.35	15,201,000	29.34	32,166,000
Total	44,239,000	100.00	51,821,000	100.00	

*Based on U.S. Census figures for the total male and female population ≥ 35 years of age (USDC, 1982) and the percentage of never smokers, ex-smokers and current smokers of all races ≥ 35 from the 1979/1980 National Health Interview Survey.

partly because the half-life of cotinine is substantially shorter for current than never smokers (Kyerematen *et al.*, 1982; Lynch, 1984; Sepkovic *et al.*, 1986), so that cotinine levels could underestimate the relative exposure received by the lungs of smokers. However, the major problem with using cotinine to determine relative exposures is due to the occurrence of nicotine in a protonated form in the particulate phase of the mainstream smoke inhaled by smokers but in an unprotonated form in the gas phase of the sidestream smoke inhaled by nonsmokers (Eudy *et al.*, 1986; IARC, 1985). Consequently, cotinine or nicotine levels in smokers measure the lung's particulate exposure, whereas these levels in nonsmokers largely measure nasal and pharyngeal exposure to gas phase constituents with a similar retention rate to that of nicotine. The two estimates of exposure are not comparable because they differ both by site and type of exposure. Nonsmokers should also absorb a higher percentage of inhaled nicotine than smokers because the unprotonated nicotine of sidestream smoke is absorbed more rapidly than the protonated nicotine of mainstream smoke (IARC, 1985).

Data Sources and Assumptions

Though superficially simple, the calculation of each of the four preliminary estimates is based on a large number of estimated parameters. These parameters are obtained from published data and analyses of the 1970 (NCHS, 1970) and 1979/1980 National Health Interview Surveys (NCHS, 1981). Due to the large sample size of the National Health Interview Surveys (the 1970 and 1979/1980 NHIS contain smoking data for a sample of 74,451 and 37,604 individuals ≥ 17 years of age, respectively), these surveys provide the best available estimates of the number of never, ex-, and current smokers by occupation, age, and sex (Table 1). Studies of ambient particulate ETS levels in white-collar workplaces in the U.S. are identified from the Building Performance Database, an on-line database accessible through national data networks (Sterling *et al.*, 1985). Most of the identified studies were conducted by the National Institute for Occupational Safety and Health.

All four preliminary estimates are based on estimated average exposures and risks for never and current smokers in 1980. The best exposure-based risk estimate would compare cumulative lifetime exposure for never and ever smokers, because the lifetime exposure of many ex-smokers exceeds that of current smokers. Unfortunately, no cumulative lifetime exposure data for a representative sample of ever and never smokers exists. The estimated risk and the number of excess lung cancer deaths are given for never smokers age 35 and over because almost all lung cancer deaths occur in this age group. However, the average exposure is calculated for never smokers ≥ 17 years of age. ETS exposure is more frequent among young adults (Friedman *et al.*, 1983), and this early exposure could latently affect the lung cancer risk.

In addition to many minor assumptions concerning the accuracy and representativeness of the data, the final estimate of the number of never smoker lung cancer deaths from exposure to particulate ETS is based on four major assumptions:

1. The carcinogenicity of tobacco smoke depends upon exposure to the particulate phase,
2. The lung cancer risk per unit exposure to mainstream and sidestream particulate tobacco smoke is the same,
3. The relationship between risk and each unit of exposure is approximately linear, and
4. There is no low exposure threshold where the lung cancer risk falls to zero.

Calculation of the Linear Extrapolation Estimate

The following three sections calculate the average particulate ETS exposure for never smokers and current smokers as well as the lung cancer risk for current smokers. The population of never smokers, estimated from the 1979/1980 National Health Interview Survey, is given in Table 1.

Never Smoker's Average Particulate ETS Exposure

Almost all particulate ETS exposure occurs indoors

Table 2. Estimated time budgets (hours/day)[a] in 1980 in the U.S.

Location	Employed Women	Employed Men	Housewives	All Women	All Men
In homes (their own and others)	16.3	14.1	21.3	18.6	15.7
Workplace	4.7	6.1	0.0	—	—
Places of business and other locations	1.3	1.4	1.5	1.5	1.3
Restaurants and bars	0.3	0.5	0.1	0.2	0.4
Outside of homes and in transit	1.4	1.9	1.1	—[b]	—
	24.0	24.0	24.0		

[a]The 1965 data from Szalai (1972) are adjusted to account for a 9% drop in the average hours worked between 1965 and 1980 (USDC, 1981). The reduction in work time, 0.6 hours for men and 0.5 hours for women, is divided among the time spent in the four other locations.
[b]No exposure is assumed for this category.

because of low indoor ventilation rates and because adults spend over 85% of their time indoors (Szalai, 1972). The average never smoker's exposure to particulate ETS depends on 1) the average inhalation rate and, for each indoor location, 2) the time spent there, 3) the average particulate ETS level, and 4) the proportion of never smokers exposed.

1. Inhalation rate

Data from Altman and Ditmer (1971) indicate an average inhalation volume of 1.08 m^3/hour for men and 0.62 m^3/hour for women, based on the average volume of air inhaled at rest and during light work.

2. Time spent in five locations

The results of a 1965 44-city time budget study (Szalai, 1972) are used to estimate the average daily time spent by never smokers in five locations; home, work (including time before and after work and during lunch), places of business and other locations, restaurants and bars, and outside the home and in transit. The time spent in restaurants and bars is determined separately, because they sometimes have very high ambient particulate ETS levels. Unfortunately, the original data do not permit dividing time into indoor and outdoor hours — time spent in both "places of business and other locations" and "outside of home and in transit" includes indoor and outdoor locations. To simplify matters, we assume that all time spent in "places of business and other locations" is indoor time where particulate ETS exposure occurs and all time spent "outside of home and in transit" is outdoor time with no particulate ETS exposure.

Table 2 estimates the average time spent in each location by employed men, employed women, and housewives. The time budget for housewives is used to estimate the time budget for all nonemployed men and women ("nonemployed" includes individuals actively seeking work, homemakers, and retirees). Time spent in nonwork locations is adjusted for the proportion of nonemployed adults because, according to time budget results, housewives spend more time in places of business and less time in restaurants and bars than do employed individuals. The 1979/1980 National Health Interview Survey estimates that 19.1% of male and 49.2% of female never smokers are nonemployed. Table 2 also gives the employment-weighted time spent in each nonwork location.

3. Indoor particulate ETS levels

Indoor particulate ETS exposure is indirectly estimated from on-site measurements of total or respirable suspended particles. This method requires an adjustment for background (nonsmoking-related) particulate levels. Background measurements should be taken indoors when no one has smoked for several hours but when all other conditions are the same as during periods of smoking (these criteria are rarely met). If there are no indoor background measurements, outdoor measurements are used as a crude estimate of the indoor particulate level in the absence of smoking.

Estimated particulate ETS levels in restaurants and bars. The average particulate level (unadjusted for background levels) in 27 restaurants, bars and entertainment facilities is 0.30 mg/m^3 (see Table 3). The average indoor particulate ETS level, after adjusting for the average background particulate level of 0.04 mg/m^3, is 0.26 mg/m^3.

Estimated particulate ETS levels in places of business. The estimated average particulate ETS level in offices (see below) is also used for the time budget category "places of business and other locations" (banks, shopping centers, etc.).

Estimated particulate ETS levels in the workplace. Workplace particulate levels are available for restaurants, bars, offices, and service buildings. It is impossible to estimate particulate ETS exposures from particulate levels in indoor blue-collar workplaces because of high background particulate levels from industrial activities. The average particulate ETS exposure should be less for blue-collar than white-collar never smokers because blue-collar workplaces, compared to offices, are better ventilated in order to re-

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Table 3. Particulate levels (mg/m^3) in bars, restaurants and entertainment facilities in the U.S.

Reference	Premise	Measurement Type	#	Mean	Background (# measurements)
Cuddeback *et al.*, 1976	2 Taverns	TPM[a]	5	0.445	(none)
Elliot & Rowe, 1975	3 Arenas	TPM	19	0.367	0.07 (2 indoors)
First, 1984	3 Taverns	nd[b]	nd	0.543	(none)
	3 Restaurants	nd	nd	0.220	(none)
Repace & Lowrey, 1980	17 Entertainment facilities[c]	RSP[d]	20	0.243	0.04 (4 indoors)
			Average:[e]	0.30	
		Adjusted for background levels:[f]		0.26	

[a]Total particulate matter.
[b]No data given.
[c]Three bars, seven restaurants, and one each of a lodge, bar and grill, firehouse bingo game, church bingo game, inn, bowling alley, and an arena. Active smoking occurred during the time of all measurements.
[d]Respirable suspended particles.
[e]The average is determined by weighting for the number of premises in each study.
[f]Adjusted for Repace and Lowrey's (1980) background level of 0.04 mg/m^3. The background level of Elliot and Rowe is not used because it is for arenas which make up only a small proportion of high exposure workplaces.

duce dust and fume exposure and because smoking is prohibited in a higher percentage of blue-collar workplaces (NICSH, 1978). However, we assume that exposed blue-collar workers receive the same particulate ETS exposure as white-collar office workers.

Table 4 summarizes the results of twenty studies of particulate levels in office or service buildings in the U.S. The mean total and respirable particulate levels are 0.08 mg/m^3 and 0.068 mg/m^3, respectively. The overall mean particulate level, ignoring the difference between total and respirable particulates, is 0.076 mg/m^3. The mean level, limited to twelve studies where active smoking was reported to occur during the time of measurement, is also 0.076 mg/m^3.

Outdoor background levels, reported by seven studies, average 0.053 mg/m^3 and range from 0.01 to 0.1 mg/m^3. The indoor background level in the absence of active smoking is 0.035 mg/m^3 in two studies of offices (Parker *et al.*, 1983; Collett, 1985) and 0.037 mg/m^3 in one study of an office and two libraries (Repace and Lowrey, 1980).

The minimum background outdoor particulate level of 0.01 mg/m^3 is used to conservatively estimate the indoor particulate ETS level because indoor particulate levels for 13 studies are below the outdoor average of 0.053 mg/m^3 while in eight studies the indoor particulate level is below the indoor background level of approximately 0.035 mg/m^3. Therefore, up to 0.066 mg/m^3 (0.076–0.01) of airborne particles in office and service buildings could be from tobacco smoke, assuming no other indoor sources of particles.

Estimated particulate ETS levels in residences. Five field studies measure the effect of at least one smoker on the 24-hour particulate level in residences. Table 5 shows that one smoker increases the hourly particulate level over background levels (homes with no smokers) by an average of 0.015 mg/m^3, while two smokers increase the particulate level by an average of 0.042 mg/m^3. The latter average is assumed to represent all residences with two or more smokers.

The average home exposure is weighted by the proportion of never smoking respondents to the 1970 National Health Interview Survey who reported living with one versus two or more smokers. The weighted average hourly particulate ETS level in the residences of never smokers is approximately 0.02 mg/m^3 for both sexes.

4. Proportion of never smokers exposed in each location

All never smokers are assumed to be exposed in "restaurants and bars" and "places of business and other locations." The proportion exposed at work is estimated from the occupational distribution of never smokers while the proportion exposed at home is estimated from the proportion of never smokers who report living with a current smoker (spouse, relative, friend, etc.).

Proportion of never smokers exposed at work. Table 6 gives the 1979/1980 National Health Interview Survey employment distribution of never smokers age 17 and older. Occupations are grouped by the likelihood of particulate ETS exposure. Students are categorized as working in indoor white-collar environments, while blue-collar workers are separated into outdoor and indoor workers. All white-collar, indoor blue-collar, and restaurant and bar employees are assumed to be exposed to particulate ETS at work, while nonemployed individuals and outdoor workers are assumed to receive no workplace exposure. In total, 66.7% of all male and 49.3% of all female never smokers are estimated to be exposed to particulate ETS at work.

Proportion of never smokers exposed at home. The

Table 4. Particulate levels (mg/m³) in white-collar workplaces in the U.S.

Reference	Use	Building Smoking[a]	Employees[b]	Measurement Type	#	Length	Date	Mean
Blake *et al.*, 1981	Store	nd	nd	TPM	10	nd	Nov/79	0.019
Chrostek, 1979	Office	nd	30	RSP[c]	1	7 hr	May/79	0.030
Chrostek & Moshell, 1982	Office	nd	100	TPM	5	8 hr	Aug/81	0.120
Collett, 1985	Office	Y	6[d]	RSP	8	40 min	Jul/85	0.050
Cornwell *et al.*, 1981	Office	Y	>100	RSP	28	2 min	Nov/80	0.048
Gorman, 1980	Office	nd	6	TPM	nd	nd	Jul/80	0.11[f]
Gunter & Thoburn, 1985	Office	nd[f]	nd	TPM[g]	7	6.5 hr	Nov/84	0.164
Hicks, 1981a	Office	Y	nd	nd	3	nd	Mar/80	0.047
Hicks, 1981b	Office	nd	40	TPM	2	6 hr	Dec/80	0.055
Hodgson & Morley, 1983	Office	nd	41	RSP	3	nd	Mar/83	0.025
Hollett, 1979	Office	nd	nd	TPM	21	nd	Jul/79	0.143[h]
Moschandreas *et al.*,	Office	Y	150	TPM	3	24 hr	nd	0.030[i]
1980	Office	Y	100	TPM	3	24 hr	nd	0.038[j]
Neal *et al.*, 1978	Hospital	Y	nd	TPM	41	48/hr	Aug–Feb	0.030
Parker *et al.*, 1983	Office	Y	100	TPM	2	8 hr	Feb/83	0.032
	Office	Y	16	TPM	3	8 hr	Feb/83	0.094
Repace & Lowrey, 1980	Hospital waiting room	Y	nd	RSP	1	12 min	Mar	0.187
Salisbury, 1979	Stock Exchange	Y	nd	TPM	3	5 hr	Oct/78	0.287
Salisbury *et al.*, 1982	Office	Y	500	TPM	8	6 hr	Mar/81	0.038
Tharr, 1980	Office	nd	100	TPM	2	7 hr	Jun/80	0.060
Thompson *et al.*, 1973	2 stores	nd	nd	TPM	nd	nd	Nov/71	0.083
Turiel *et al.*, 1981	Office	Y	nd	TPM	nd	12 hr	nd	0.031
							Average:	0.076
			Adjusted for Background Level (see text):					0.066

[a]Active smoking while particulate levels were sampled.
[b]On the floor(s) where measurements taken.
[c]Respirable suspended particles.
[d]In immediate area of sampler, two of the six staff were smokers.
[e]Close to office copier.
[f]No data given.
[g]Total particulate matter.
[h]Major construction site across the street.
[i]Based on 24 hour sample. Maximum recorded 0.057 mg/m³.
[j]Based on 24 hour sample. Maximum recorded 0.130 mg/m³.

Table 5. Effect of smoking on 24-hour respirable suspended particle (RSP) levels (mg/m³) in residences in the U.S.

Reference	Mean RSP Level in Homes with			Increase due to	
	No Smokers	1 Smoker	2 Smokers	1 Smoker	2 Smokers
Spengler *et al.*, 1981	0.024	0.037	0.052	0.012	0.027
EPRI, 1984	0.024	0.043	0.075	0.019	0.051
Hosein & Corey, 1986[a]	0.038	0.053	0.080	0.015	0.042
Lebowitz *et al.*, 1984	0.018	0.033[b]	—	0.015	—
Spengler *et al.*, 1985	0.028	—	0.074[b]	—	0.046
			Average:	0.015	0.042

[a]Average of reported winter and summer means.
[b]Number of resident smokers not given in reference. The results have been assigned to the most probable category, on the basis of the results of the other studies.

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Table 6. 1979/1980 National Health Interview Survey estimate of the occupational distribution of never smokers ≥ age 17 in the U.S.

Occupation	Men (%)	Women (%)
Indoor white-collar[a]	43.3	41.0
Indoor blue-collar[b]	21.6	6.2
Restaurants and bars[c]	1.8	2.1
Outdoor workers[d]	14.2	1.5
Not employed[e]	19.1	49.2
	100.0	100.0

[a]Includes students and professional, managerial, technical, clerical and service occupations.
[b]Includes industrial and warehousing occupations.
[c]Includes waiters and waitresses, entertainers, bartenders, busboys, recreation and amusement attendants, pub and food service workers.
[d]Includes construction, agriculture, forestry and fishing occupations.
[e]Includes retired, homemakers and unemployed.

1970 National Health Interview Survey estimates that 29.6% of male and 35.7% of female never smokers age 17 and over live with a current smoker. Since the 1979/1980 National Health Interview Survey does not include smoking information for all household members, it cannot be used for this purpose. However, using data for 1970 should overestimate the proportion of never smokers exposed at home in 1980 because the number of active smokers has declined 6% for men and 2% for women between 1970 and 1980 (Weinkam & Sterling, 1987).

Estimated particulate ETS exposure

Table 7 summarizes the average never smoker's inhalation exposure to particulate ETS. The average daily inhaled particulate ETS exposure is 0.62 mg for male and 0.28 mg for female never smokers. The daily retained particulate ETS exposure, based on an 11% retention rate, is 0.07 mg for male and 0.03 mg for female never smokers.

Current Smoker's Average Exposure

The average smoker's daily exposure to particulate tobacco smoke is assumed to equal the average number of cigarettes per day consumed multiplied by the average tar delivery per cigarette. For simplicity, the current smoker's particulate ETS exposure is not included because it is only a small fraction of the current smoker's total particulate tobacco smoke exposure. An average consumption of 29.3 cigarettes per day for current smokers is calculated by dividing the 1979/1980 average of 626.5 billion cigarettes sold in the U.S. (Maxwell, 1981) by the 1979/1980 National Health Interview Survey estimate of 58.5 million current smokers age 17 and over. The average of 29.3 cigarettes per day is used for both sexes because there is little difference in the 1979/1980 National Health

Table 7. Estimate of the average never smoker's inhalation exposure of particulate environmental tobacco smoke (ETS) (mg/day) in 1980 in the U.S.

Location	Respiration Rate/hour	Ambient ETS mg/m³	Hours of Exposure	Proportion Exposed	Weighted Exposure
Men					
Home	1.08	0.02	15.7	0.296	0.100
Rest/Bar[a]	1.08	0.26	0.4	1.000	0.112
Other[b]	1.08	0.066	1.3	1.000	0.093
Work					
White-collar	1.08	0.066	6.1	0.433	0.188
Blue-collar	1.08	0.066	6.1	0.216	0.094
Rest/Bar	1.08	0.26	6.1	0.018	0.031
No Workplace Exposure[c]	—	—	—	0.333	0.000
					Total 0.62
Women					
Home	0.62	0.02	18.6	0.357	0.082
Rest/Bar	0.62	0.26	0.2	1.000	0.032
Other	0.62	0.066	1.5	1.000	0.061
Work					
White-collar	0.62	0.066	4.7	0.410	0.079
Blue-collar	0.62	0.066	4.7	0.062	0.012
Rest/Bar	0.62	0.27	4.7	0.021	0.016
No Workplace Exposure	—	—	—	0.501	0.000
					Total 0.28

[a]Restaurants and bars.
[b]Places of business and other locations.
[c]Unemployed, retired, homemakers, and outdoor workers.

The average lung cancer risk for all current versus all ex-smokers is 2.26, based on a risk of 1.67 in the American Cancer Society study and 2.85 in the Veterans study. The average ratio of 2.26, combined with the 1979/1980 National Health Interview Survey estimates of the number of current and ex-smokers, predicts 20,517 male and 4,410 female ex-smoker lung cancer deaths.

The difference in the risks for ex-smokers compared to current smokers in the two studies is probably due to the higher percentage of long-term ex-smokers, with lower lung cancer rates than short-term ex-smokers, in the Veterans study. All ex-smokers in the Veterans study had not smoked for a minimum of twelve years compared to a minimum of 34 months for ex-smokers in the American Cancer Society study. The American Cancer Society results may be more appropriate here because the National Health Interview Survey estimate of the number of ex-smokers includes both short and long-term ex-smokers.

Current smoker lung cancer deaths not attributable to smoking

The number of nonsmoking-attributable current smoker lung cancer deaths is estimated by assuming that smokers would experience the mortality rates of the National Morality Followback Survey never smokers if they did not smoke. These mortality rates, applied to the 1979/1980 National Health Interview Survey estimate of the sex and age-specific population of current smokers, estimate 3,111 male and 1,094 female lung cancer deaths.

Smoking attributable lung cancer risk for current smokers

The number of smoking-attributable lung cancer deaths among male current smokers over 35 is 48,255, obtained from subtracting 3,479 never smoker, 20,517 ex-smoker, and 3,111 nonsmoking-attributable lung cancer deaths among current smokers from the 1980 total of 75,362 male lung cancer deaths. The same method estimates 18,394 smoking-attributable lung cancer deaths among female current smokers over 35 in 1980. Given 16.965 million male and 15.201 million female current smokers over 35 in 1980, this estimates a smoking-attributable lung cancer risk of 284 lung cancer deaths (LCD)/100,000 male and 121 LCD/100,000 female current smokers over age 35. Repace and Lowrey (1985) estimate a rate of 316 LCD/100,000 male or female smokers for use in their linear extrapolation estimate. However, they assume that all smoking-attributable lung cancer deaths occur among current smokers only (no deaths among ex-smokers), they do not adjust for occupational or other causes of lung cancer among smokers, and they include cancers of the larynx and other non-lung sites.

Lung Cancer Risk for Never Smokers From Particulate ETS Exposure

The estimated daily retained exposure is 310 mg for male and 249 mg for female current smokers and 0.07 mg for male and 0.03 mg for female never smokers. The male smoker's retained exposure is 4,429 times greater than the average male never smoker's retained exposure. Given a smoking-attributable lung cancer death rate for male current smokers of 284 LCD/100,000, the average male never smoker's lung cancer risk is 0.064 LCD/100,000, which predicts approximately 8 lung cancer deaths from exposure to particulate ETS among the 11.96 million male never smokers in 1980. The same method estimates a risk of 0.015 LCD/100,000 female never smokers, which predicts 4 lung cancer deaths from exposure to particulate ETS among the 28.85 million female never smokers in 1980.

Reliability of the Estimate

The linear extrapolation estimate of 12 never smoker lung cancer deaths in 1980 from exposure to particulate ETS is based on a large number of unverifiable assumptions and parameter estimates. Due to the large number of assumptions, it is neither meaningful nor possible to calculate upper and lower confidence limits. However, the reliability of each of the four preliminary estimates is assessed below. Evidence indicates that several of the preliminary estimates are more likely to result in an overestimate rather than an underestimate of the true number of never smoker lung cancer deaths. However, a plausible upper estimate is calculated for three of the four preliminary estimates. These upper estimates are used to calculate a maximum final estimate, given the major assumptions of the linear extrapolation method.

Number of Never Smokers

The final estimate of the number of never smoker lung cancer deaths increases if the estimated number of never smokers increases. The present estimate of 11.96 million male and 28.85 million female never smokers is based on self-reported smoking status, and is probably an overestimate of the number of never smokers. Two-stage interview studies show that approximately 5% of self-reported never smokers are actually ex- or current smokers (NRC, 1986). For this reason, the estimated number of never smokers is not increased when calculating the upper estimate.

Never Smoker's Average Exposure

The estimated number of never smoker lung cancer deaths increases if the average never smoker's exposure increases. Several factors suggest that our estimated exposure *overestimates* the true exposure. For

example, many of the measurements of total or respirable particles are for workplaces which probably had higher than average particulate ETS levels. Most buildings in the Building Performance Database were studied in response to occupant complaints about "building illness" or poor indoor air quality. Even though tobacco smoke may not be an important factor in building illness (Sterling *et al.*, 1987), it could affect the occupants' perception of the air quality and lead to more complaints in buildings with high versus low particulate ETS levels. In addition, all indoor blue- and white-collar workers are assumed to be exposed to particulate ETS at work, even though smoking is prohibited in 11% of white- and 28% of blue-collar workplaces (NICSH, 1978). Interview studies also show lower workplace exposure rates than the estimated rate of 66.7% for male and 49.3% for female never smokers. For example, only 29.4% of the control group of female never smokers in a case-control study report workplace exposure during the past 25 years (Garfinkel *et al.*, 1985). In a 1979/1980 questionnaire survey of 37,881 never smokers, only 40.4% of both sexes combined reported ETS exposure in "small spaces" such as at work (Friedman *et al.*, 1983).

Two field studies contain enough information to calculate the average inhaled particulate ETS exposure for men. Both of these studies estimate average particulate ETS exposures that are within six percent of the comparable estimates given in Table 7. The studies use personal monitors, carried by subjects for several days, to determine average exposures to respirable suspended particles. The difference between the average personal and background (outdoor) exposures to respirable suspended particles in a study of 48 subjects, none of whom live with a smoker, is 0.019 mg/m^3 (Sexton *et al.*, 1984). If particulate ETS accounts for all of the difference in respirable suspended particles, then the average 24-hour particulate ETS exposure at a male respiration rate of 1.08 m^3/hour, is 0.49 mg/day. For comparison, our estimate of the average daily inhaled exposure of male never smokers with no home exposure is 0.52 mg/day (see Table 7). Spengler *et al.* (1985) determine personal exposures to respirable suspended particles for 101 volunteers in two industrial towns in Tennessee. The difference between the average personal exposure and the background (outdoor) level is 0.024 mg/m^3. This predicts an average daily particulate ETS exposure of 0.62 mg/day, which is identical to our estimate for men.

Repace and Lowrey (1985) estimate an average inhaled exposure for either sex of 1.43 mg/day, based on modeling indoor smoking, occupancy, and ventilation rates, which is 3.18 times the average of our estimates for men and women. There are several possible causes for the difference. For example, Repace and Lowrey assume that all never smokers are actively employed and, therefore, possibly exposed at work. In contrast, the 1979/1980 National Health Interview Survey estimates that approximately 40% of all never smokers are not employed. Furthermore, Repace and Lowrey calculate the average ambient ETS level in the workplace from the average of modeled levels in low-exposure and high-exposure workplaces. Their model estimates an ambient particulate level (from tobacco smoke alone) of 0.17 mg/m^3 for low-exposure workplaces such as offices and of 0.42 mg/m^3 for high-exposure workplaces. The particulate level for the latter is representative of measured levels in very smoky workplaces such as taverns, bars, and dance halls. The average for the two types of workplaces is 0.30 mg/m^3, which is higher than all of the measured levels for white-collar workplaces (see Table 4) and higher than the average for restaurants, bars and other entertainment facilities (see Table 5). It may not be appropriate to average the estimate for low and high-exposure workplaces, because the 1979/1980 National Health Interview Survey estimates that approximately twenty times as many never smokers work in low-exposure workplaces such as offices than in high-exposure workplaces such as bars and taverns.

There is no plausible average upper estimate for the inhaled exposure which is substantially greater than the estimates given in Table 7, which is also based on field measurements of ambient particulate levels. However, an arbitrary upper estimate can be made by doubling the previous estimates. Thus, the upper inhaled estimates are 1.24 mg/day for male and 0.56 mg/day for female never smokers. These give average retained exposures of 0.14 mg/day for male and 0.06 mg/day for female never smokers.

Current Smoker's Average Exposure

The estimated number of never smoker lung cancer deaths increases if the average smoker's true exposure, derived from the average tar delivery per cigarette multiplied by the average cigarette consumption, is *less* than estimated.

The average tar delivery per cigarette is based on machine smoked deliveries. The machine smoking standard of one two-second 35 ml puff/minute was established over 30 years ago to reflect the smoking habits of that time. Since then, several studies indicate that smokers partially compensate for a decline in the nicotine delivery per cigarette by smoking each cigarette more intensely (Ashton *et al.*, 1979; Herning *et al.*, 1981; Hill & Marquardt, 1980; Russell *et al.*, 1975). This is done by increasing the average puff frequency and/or volume or by inhaling more deeply. The probable increase in the intensity with which cigarettes are smoked indicates that the estimated exposure for current smokers is more likely to *underestimate* than overestimate the true exposure.

Conversely, the average consumption of 29.3 ciga-

rettes per day is based on sales data for the number of cigarettes sold in 1980 divided by the 1979/1980 National Health Interview Survey estimate of the number of current smokers. Estimates based on interviews with current smokers are not used because smokers significantly underreport their cigarette consumption (Todd, 1978). However, the estimate of 29.3 cigarettes per day may be too high because the 1979/1980 National Health Interview Survey excludes smokers under age 17 and because some of the self-reported never and ex-smokers should be current smokers (NRC, 1986). If the probable increase in smoking intensity is ignored, an increase in the estimated number of current smokers by 10% (to account for smokers under age 17 and misclassified never smokers) decreases the average daily retained exposure from 310 mg to 283 mg for male and from 249 to 228 mg for female current smokers. This is further decreased to 166 mg for male current smokers and to 134 mg for female current smokers by using the lowest experimentally determined particulate retention rate of 47% (First, 1984) instead of an 80% retention rate.

Current Smoker's Average Lung Cancer Rate

The estimated number of never smoker lung cancer deaths increases if the lung cancer risk for current smokers increases. This occurs if the estimated number of lung cancer deaths decreases among (1) ex-smokers, (2) never smokers, and (3) current smokers who die from causes other than smoking. This is calculated for the latter two groups by using the American Cancer Society never smoker lung cancer death rates (Garfinkel, 1981) instead of the rates from the National Mortality Followback Survey. The American Cancer Society rates were not used before because they are for an unrepresentative group of mostly middle-class individuals (Hammond & Seidman, 1980), whereas the National Mortality Followback Survey rates are based on a representative sample of all never smoker lung cancer deaths. The number of ex-smoker lung cancer deaths is minimized if the ex-smoker/smoker mortality ratio from the Veterans study (Rogot & Murray, 1980) is used instead of the average for the American Cancer Society and Veterans studies combined.

These three changes increase the estimated number of current smoker lung cancer deaths from 48,255 to 55,902 male deaths and from 18,394 to 19,954 female deaths. However, this only slightly alters the lung cancer risk because the revised estimate of the average smoker's exposure depends upon increasing the number of smokers by 10%. Given a 10% increase in smokers, the lung cancer rate increases 5.6% to 300 LCD/100,000 male never smokers, but falls 1.7% to 119 LCD/100,000 female never smokers.

The lung cancer death rate for female current smokers is substantially less than the rate for male current smokers. The difference could partly be caused by women inhaling less deeply than men or by smoking lower tar cigarettes. Alternatively, the lower mortality rate for women could reflect a shorter latency period because women, on average, took up smoking at a later date than men. An upper estimate of the lung cancer death rate for female smokers can be adjusted for this by assuming that the risk/mg of exposure for women is equal to the risk/mg of exposure for men. This estimates a risk of 242 LCD/100,000 female smokers.

Upper Risk Estimate

The upper estimate is 62 lung cancer deaths among never smokers as a result of exposure to particulate ETS. This is based on a lung cancer death rate of 300 LCD/100,000 male and 242 LCD/100,000 female current smokers, an average retained exposure of 166 mg/day for male and 134 mg/day for female current smokers, and a retained exposure of 0.14 mg/day for male and 0.06 mg/day for female never smokers.

Comparison with Other Estimates

The linear extrapolation estimate of 12 deaths, or the upper linear extrapolation estimate of 62 never smoker lung cancer deaths, is substantially less than five alternative estimates, ranging from 265 to 3,610 lung cancer deaths, given in Table 9. All of the alternative estimates use the National Health Interview Survey estimate of the number of never smokers $\geq$ 35 years of age. Three of the alternatives are risk-based estimates derived from the results of epidemiological studies: one from the difference in lung cancer mortality rates between Seventh-Day-Adventists and other never smokers (termed a phenomenological estimate by the authors), and the other two apply average geometric mean lung cancer risks observed in epidemiological studies to the population-attributable risk equation (Cole & MacMahon, 1971). The two remaining estimates are exposure-based estimates derived from smoker/never smoker exposure ratios and linear extrapolation.

To a certain extent, differences among the various estimates are expected because each type of estimate (for example, linear extrapolation or population-attributable risk methods) requires different assumptions and all estimates are only crude approximations without confidence limits. However, even if the confidence limits for all estimates include all other estimates, this does not explain the 22- to 301-fold difference between the linear extrapolation estimate of 12 lung cancer deaths and the other estimates.

The previous discussion shows that the substantial difference between our estimates and the alternative estimates cannot be adequately explained by errors in our estimates of the number of never smokers, the average exposure for current and never smokers, or

Table 9. Alternative estimates of the number of ETS-attributable never smoker lung cancer deaths (LCD) (both sexes combined) in 1980 in the U.S.

Method	Description	Estimated LCDs
Phenomenological	Repace and Lowrey's (1985) sex and age-specific difference in LCD rates between Seventh-Day-Adventist (SDA) and non-SDA never smokers is applied to the 1979/1980 National Health Interview Survey estimate of the U.S. population of never smokers by sex and age (Arundel *et al.*, 1986).	3,610
Linear Extrapolation Based on ETS Exposure	Repace and Lowrey's (1985) estimate of 555 nonsmoker (never and ex-smokers combined) LCDs is adjusted for the National Health Interview Survey estimate of the percentage (63.87%) of nonsmokers that are never smokers.	354
Linear Extrapolation Based on Cotinine Ratios	The estimated smoking-attributable LCD rate for current smokers of 284 LCD/100,000 men and 121 LCD/100,000 women is divided by the ratio of the weighted average urine cotinine level of 1483.7 ng/ml for smokers and 5.72 ng/ml for never smokers in four studies (Williams *et al.*, 1979; Kyerematen *et al.*, 1982; Jarvis *et al.*, 1984; Wald *et al.*, 1984).	265
Population Attributable Risk (PAR) Estimates*		
RR is 1.35	*RR* is Wald's *et al.*, (1986) estimate of the geometric mean risk observed in 13 epidemiological studies from six countries. The risk is 1.53 for never smokers living with smokers and 1.18 for never smokers not living with smokers, after adjustment for the misclassification of 7% of ever smokers as never smokers and a relative difference in ETS exposure of 3.0 (Wald & Ritchie, 1984) for the two groups of never smokers. *p* is 0.249 for male and 0.505 for female never smokers (see text). The average PAR is 0.21 for male and 0.26 for female never smokers.	1,852
RR is 1.14	*RR* is the geometric mean risk observed in 5 epidemiological studies from the U.S. only (NRC, 1986). The risk is 1.16 for never smokers living with a smoker and 1.05 for never smokers living with never smokers after adjustment for a misclassification rate of 6%, a risk for misclassified ever smokers of 2.0 and a threefold exposure difference for the two groups of never smokers. *p* is 0.249 for male and 0.505 for female never smokers. The average PAR is 0.072 for male and 0.094 for female never smokers.	655

*The adjusted PAR equation (Eq. 5, p. 292, NRC, 1986) equals:

$$\frac{p_1(RR_1-1)+(1-p_1)(RR_2-1)}{p_1(RR_1)+(1-p_1)(RR_2)}$$

where p_1 is the proportion of never smokers who live with an ever smoker, RR_1 is the risk for never smokers who live with an ever smoker and RR_2 is the risk for never smokers who live with never smokers. The PAR × N, the total number of never smoker LCDs in 1980 (3,479 male, 4,312 female (Table 8)), gives the estimated number of never smoker lung cancer deaths from ETS exposure. The estimates are calculated for each sex and then summed.

the lung cancer risk for current smokers. On the contrary, there is also evidence to indicate that the estimate of 12 lung cancer deaths is too high. The difference cannot be due to an error in the estimated number of never smokers because all estimates are based on the National Health Interview Survey estimate of the population of never smokers ≥ 35 years of age. There are two possible explanations for the difference: either the alternative estimates given in Table 9 overestimate the true risk, or there are major problems with one or more of the four major assumptions underlying the linear extrapolation estimate, which causes it to underestimate the true risk.

Alternative Estimates

Several features of the two alternative linear estimates indicate that they could overestimate the true risk. The estimate based on cotinine ratios assumes that cotinine levels in the blood or urine of smokers

and nonsmokers measure comparable exposures. As discussed earlier, this assumption is probably not valid. Cotinine in smokers measures the lung's exposure to particulate tobacco smoke, whereas cotinine in nonsmokers measures nasal and pharyngeal exposure to the gas phase. Neither the site nor type of exposure is comparable. Repace and Lowrey's (1985) linear extrapolation estimate could also overestimate the true risk from ETS exposure because it appears to overestimate both the never smoker's average exposure and the average smoker's lung cancer risk. The method also uses the inhaled exposure instead of the retained exposure.

The alternative risk-based estimates depend on epidemiological estimates of the lung cancer risk from ETS exposure. The phenomenological estimate is based on a risk of 1.73 for male and 2.54 for female never smokers, calculated from the difference in lung cancer mortality rates for Seventh-Day-Adventist nonsmokers and another group of nonsmokers. The method assumes that the Seventh-Day-Adventists received less exposure to ETS than the other group of nonsmokers. However, the mortality rates for the Seventh-Day-Adventists are based on only 15 female and 10 male deaths. Consequently, these rates are unstable, with large fluctuations in the death rates instead of a consistent increase with each successive age group. These fluctuations could lead to an overestimate of the lung cancer risk from ETS exposure (Arundel *et al.*, 1986).

The population-attributable risk estimates are based on only three parameters: the geometric mean lung cancer risk from ETS exposure, the proportion of never smokers exposed to ETS, and the number of never smokers at risk. The difference between the population-attributable risk and linear estimates cannot be attributed to errors in the estimated value of the number of never smokers at risk because this parameter is also used in the linear estimate. Both methods also assume that all never smokers are exposed to ETS, though the population-attributable risk method calculates separate risks for the proportion of never smokers exposed to ETS at home and the proportion not exposed at home. These proportions are derived from the 1970 National Health Interview Survey estimate that 24.9% of male and 50.5% of female never smokers age 35 and over live with a current or former smoker.

The population-attributable risk method, based on a geometric mean risk of 1.35 from 13 epidemiological studies, estimates 1,852 lung cancer deaths in 1980 among never smokers from exposure to ETS. The method is similar to that used by Robins (1986). Robins' method estimates 1,807 lung cancer deaths in 1980 among never smokers of both sexes from ETS exposure.

The difference in the linear and population-attributable risk estimates could occur if all estimates of the geometric mean risk overestimate the true risk. Lee (1986) has shown that the misclassification of ever smokers as never smokers could result in an overestimate of the geometric mean risk. However, the population-attributable risk estimates are adjusted for misclassification, though the misclassification rate and the lung cancer risk for misclassified ever smokers is only crudely estimated. The geometric mean risk could also be biased by response or recall bias in the case-control studies on which it is based or by differences in the age distribution of lung cancer cases in the epidemiological studies and the age distribution of never smokers in the U.S. Furthermore, the geometric mean risk is a crude risk; it is not adjusted for age or any other possible or established risk factor for lung cancer such as occupation, socioeconomic status, or diet. The lack of adjustment for other risk factors could bias the geometric mean risk either upwards or downwards.

Assumptions of the Linear Estimate

Three of the four major assumptions of the linear extrapolation estimate can provide a plausible explanation of the difference between our estimate and the population-attributable risk estimates. The assumption of no low threshold, where the risk falls to zero, is irrelevant. The second assumption is that the dose-response relationship is linear. The difference between the estimates can be explained if the true dose-response relationship is nonlinear and convex, such that one unit of exposure at low doses is substantially more carcinogenic than one unit of exposure at high doses. However, most dose-response studies of chemical carcinogens have found sublinear or "hockey stick" shaped relationships between exposure and risk in which one unit of exposure at low doses results in a smaller increase in risk than one unit of exposure at high doses (Hoel *et al.*, 1983). The linear assumption is usually recommended as a conservative estimate of risk because it is believed to err towards overestimating the true risk (Anderson, 1983).

The best fitting equation for the lung cancer death rate per unit of exposure in a 1951–1971 cohort study of 34,440 British doctors is nonlinear and equal to 0.26 $(\text{dose}+6)^2$, where dose is the average number of British cigarettes smoked at the time of the study (Doll & Peto, 1978). This equation indicates that the linear assumption overestimates the risk from ETS exposure. For example, the sales-weighted average British cigarette between 1951 and 1971 delivered 29.9 mg of particulate tobacco smoke to the smoker (Wald *et al.*, 1981). An average inhaled exposure for male never smokers of 0.62 mg/day of particulate ETS (equivalent to 0.02 British cigarettes) results in an annual excess inhaled-exposure risk of 0.06 LCD/100,000 never

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Table 10. Relative particulate tobacco smoke exposure for current and never smokers in 1955, 1968 and 1980

	1955	1968	1980
Proportion of population that smoke[a]	0.376	0.386	0.345
Tobacco weight of an average cigarette (grams)[b]	1.12	0.95	0.80
Tar (including nicotine) delivery per cigarette (mg)[c]	40.1	23.1	14.2
Cigarettes/day (CPD) smoked by the average smoker[d]	26.2	29.7	29.3
Never smoker's exposure index[e]	11.0	10.9	8.1
Smoker's daily exposure (mg)[f]	1050.6	686.1	416.1
Ratio of smoker's exposure/never smoker's exposure index	95.5	62.9	51.4

[a]1955: ≥ age 18 (SG, 1979), 1968: ≥ 17 (SG, 1979), 1980: ≥ 17 (1979/1980 National Health Interview Survey).
[b](USDA, 1985).
[c]1955 and 1968 (SG, 1981), 1980 (Tobacco Inst., 1981).
[d]For 1955 and 1968, equals per capita (≥ 18) number of cigarettes sold (Table 1-1, NRC, 1986)/proportion of population who smoke/365. For 1980, equals the number of cigarettes sold/National Health Interview Survey estimate of the number of never smokers ≥ 17.
[e]Proportion of population that smoke × tobacco weight × CPD per smoker.
[f]Tar delivery per cigarette × CPD.

smokers. Adjusting for the retained exposure decreases the risk to 0.008 LCD/100,000, which predicts 1.4 lung cancer deaths among male never smokers compared to the linear estimate of 8 deaths. The same relative decline for female never smokers would estimate 0.9 female lung cancer deaths, for a combined minimum estimate of 2.3 lung cancer deaths in 1980.

The other two assumptions of the linear estimate (equal risk per unit of exposure for smokers and never smokers, and that all risk is attributable to particulate exposure) can be examined together. The difference between our estimate and the population-attributable risk estimates can be explained if ETS is substantially more carcinogenic per unit of exposure than mainstream smoke. The lowest alternative estimate of 265 lung cancer deaths requires ETS to be as much as 22 times more carcinogenic than mainstream smoke, the highest population-attributable risk estimate of 1,852 lung cancer deaths requires ETS to be as much as 154 times more carcinogenic, and the phenomenological estimate requires ETS to be as much as 301 times more carcinogenic. ETS could be more carcinogenic than mainstream smoke if there were substantial differences in the chemical composition, deposition pattern, or deposition site of passively inhaled sidestream smoke versus actively inhaled mainstream smoke.

The linear estimate is essentially based on a difference in exposure between never and current smokers, while the phenomenological and population-attributable risk estimates are based on a difference in risk between never smokers with and without regular exposure to ETS. Given the large difference in the exposure of never and current smokers, the relative risks of 2.54 and 1.73, on which the phenomenological model is based, or the relative risks of 1.34 or 1.14 used in the population-attributable risk estimates, are far too high. In our opinion, a substantially greater carcinogenicity for ETS versus mainstream smoke is the most plausible factor which could explain the large difference between our linear estimate and the risk-based estimates, assuming that the latter estimates more closely approximate the true risk. A supralinear relationship between exposure and risk could also explain the difference, though this appears less probable. Otherwise, the risk-based estimates must substantially overestimate the true risk. Further research on the relative carcinogenicity of mainstream and sidestream smoke and the dose-response relationship for low exposures to tobacco smoke is necessary.

Effect of Past Exposures

One final problem needs to be addressed. The use of the average particulate ETS exposure for never smokers in 1980 will underestimate the average never smoker's risk if the smoker/never smoker exposure ratio was less in the past than in 1980, and if past exposures are more important in the development of lung cancer than recent exposures. The latter condition may not be true: the lung cancer risk for ex-smokers declines with the number of years since smoking ceased (SG, 1979). The former condition can be examined by estimating the change in exposure over time. The average smoker's past exposure can be determined from the average cigarette consumption and the average particulate delivery. Though the average

never smoker's past exposure cannot be estimated directly, it is possible to construct a relative exposure index from annual data on the average amount of tobacco in a cigarette, the percentage of the population that smokes, and the average cigarettes per day smoked per smoker.

Table 10 gives the average smoker's exposure as well as the average never smoker's exposure index for 1955, 1968, and 1980. The smoker's exposure has declined 60.4% since 1955 (mostly due to increased filter use), whereas the never smoker's exposure index has declined only 26.4%. The faster decline for smokers means that the 1980 smoker/never smoker exposure ratio is less than the ratio in 1955 (Table 10) and that the 1980 risk estimate for never smokers should overestimate the true risk based on a composite of past exposures.

The estimated average particulate ETS exposure for current smokers in 1980, based on machine-smoked particulate ETS deliveries, would overestimate the decline in the average smoker's exposure if each cigarette is smoked more intensely in 1980 than in 1955. However, the average smoker's exposure will decline faster than the never smoker's average exposure unless the average particulate ETS delivery/cigarette in 1980 is increased by 86% to 26.4 mg. An 86% average increase in the intensity with which each cigarette is smoked is unlikely; experimental studies of smokers given cigarettes with substantially lower tar and nicotine deliveries than their usual brand find the intensity of smoking to increase by 33% to 66% (Herning *et al.*, 1981; Ashton *et al.*, 1979).

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Appendix: Equations and Parameters of the Linear Extrapolation Estimate

Never Smoker's Retained Particulate ETS Exposure:

$$\text{Exp N} = \text{NRR}(\text{ExpH} + \text{ExpR} + \text{ExpW} + \text{ExpO})$$

where:

$$\text{Home Exposure (ExpH)} = R \times LH \times PH \times AH$$

$$\text{Restaurant/Bar Exposure (ExpR)} = R \times LR \times PR \times AR$$

$$\text{Work Exposure (ExpW)} = R \times LXW(PWW \times AWW + PBW \times ABW + PRW \times ARW)$$

$$\text{Other Exposure (ExpO)} = R \times LO \times PO \times AO$$

R = the respiration rate, Lx = the length of exposure in each location x, Px = the proportion of never smokers exposed to particulate ETS in each location x, Ax = the ambient particulate ETS level in each location x, WW = white-collar workplace, BW = blue-collar workplace, NRR = the never smoker particulate ETS retention rate.

Smoker's Retained Particulate Tobacco Smoke Exposure:

$$\text{ExpSM} = \text{SMRR}(\text{CPD} \times \text{TAR})$$

SMRR = the smoker particulate tobacco smoke retention rate, CPD = the average number of cigarettes smoked/day/smoker, TAR = the average tar delivery/cigarette.

Smoker's Lung Cancer Death (LCD) Rate:

$$\text{SMLCDR} = 100{,}000(\text{NSMLCD}/\text{SMPOP})$$

where:

$$\text{NSMLCD} = \text{TLCD} - \text{LCDN} - \text{LCDEX} - \text{LCDSM}$$

NSMLCD = the number of smoking-attributable LCDs among current smokers, SMPOP = the total number of current smokers, TLCD = the total number of LCDs in1980, LCDN = number of LCDs which occurred among never smokers, LCDEX = number of LCDs which occurred among ex-smokers, LCDSM = number of LCDs which occurred among smokers from nonsmoking causes.

where:

$$\text{LCDEX} = (\text{TLCD} - \text{LCDN})/(1 + \text{NCS}/\text{NES} \times 2.26)$$

where:

NCS = the number of current smokers, NES = the number of ex-smokers.

Never Smoker's LCD Rate:

$$\text{NLCDR} = \text{SMLCDR}/(\text{ExpSM}/\text{ExpN})$$

SMLCDR = the LCD rate per 100,000 smokers, ExpSM = average smoker's particulate tobacco smoke exposure, ExpN = average never smoker's particulate ETS exposure.

Number of Never Smoker Lung Cancer Deaths from ETS Exposure:

$$= (\text{NPOP}/100{,}000)\text{NLCDR}$$

NPOP = number of never smokers, NLCDR = the lung cancer death rate per 100,000 never smokers.

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THE POTENTIAL ASSOCIATION OF LUNG CANCER WITH PASSIVE SMOKING

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The potential association of lung cancer with passive smoking has been studied epidemiologically, clinically, and with mathematical models. There have been both positive and negative studies, such that the association is still considered a potential rather than probable one. These studies, and the mathematical models, indicate that major factor in determining the relationship is the dose, and that more research is required to determine the dose side of the dose-response relationship.

Introduction

There has been a growing interest in the potential of passive (or involuntary) smoking as cause of lung cancer (Lebowitz and Apostolides, 1982). This concern is based on chemical analysis of sidestream and mainstream smoke, experiments on the effects of tobacco smoke constituents *in vitro* and *in vivo*, and some recent epidemiological evidence which may link involuntary smoking in spouses to lung cancer mortality. Since the average person spends the great majority of time indoors, it is assumed that there is a large potential for exposure to tobacco smoke generated by others (NRC, 1981).

Exposure Factors

Of the various chemicals derived from tobacco smoke, four of great concern are polycyclic aromatic matter (POM) expressed as benzo(*a*)pyrene (BaP), dimethylnitrosamines, dimethyl benz-anthracene (DMBA) and alpha-emitting radionuclides, mostly polonium 210. Comparisons of mainstream and sidestream smoke have been made by several authors (Brunneman and Hoffman, 1978; Rylander, 1974, 1984; Schmeltz *et al.*, 1975; U.S. Surgeon General, 1980). Further, at least some POM originates from other indoor sources, such as food cooking, wood burning, and other combustions (NRC, 1981). Radiation dosage does occur from cigarettes (Martell, 1974; Little *et al.*, 1965; Radford and Hunt, 1964; DiFranza and Winters, 1982); its relative contribution, to that from other sources, is still debatable (Martell, 1983; Jacobi, 1984). It has been difficult to determine the potential effects of nitrosamines or the radon progeny in the normal indoor environment on humans (Bergman and Axelson, 1983; Martel, 1983).

In vitro studies (Medical Perspectives, 1984; NRC, 1972) have shown some increased mutagenic activity of tobacco products. Studies in mice have shown that condensate from the cigarette end has tumor-producting activity greater than that leaving the mouth piece of the cigarette (U.S. Surgeon General, 1982; Wynder and Hoffman, 1967). Other experiments have been reported to show combined effects of air pollution extracts and cigarette smoke condensate when installed in or on tissue in large amounts (Hoegg, 1972). Sister chromated exchange in cultured human lymphocytes is induced by cigarette smoke condensate, though not appreciably by BaP (Hopkin, 1984).

Passive inhalation of cigarette smoke can produce tracheobronchial epithelial dysplasia and metaplasia in animals at high concentrations of smoke (Holland *et al.*, 1963; U.S. Surgeon General, 1982). The relevance to humans can be questioned because of these high levels, at excess of levels encountered by humans (Schmeltz *et al.*, 1975). ""Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains" (U.S. Surgeon General, 1982). Furthermore, human exposure experiments with sidestream smoke in unventilated rooms

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showed that air concentrations of vapor phase and particulate phase substances decreased with their presence, and the exposure of nonsmokers to tobacco smoke under realistic conditions does not appear to produce inhalation of sufficient amounts of tobacco smoke components traditionally (Holland *et al.*, 1963; Hugod *et al.*, 1978). Hiller *et al.* (1982) measured the deposition fraction of environmental tobacco smoke in humans; the mean was 11% (the median was 8%).

Only mathematical models, such as that of Repace and Lowrey (1985), appear to estimate dosage to humans from environmental tobacco smoke that may be carcinogenic. These models are based on mathematical assumptions and calculations that appear to include overestimations (Esmen, 1981). The dose so derived does not reflect estimates based on actual controlled laboratory studies (First, 1984; Hiller *et al.*, 1982; Hinds *et al.* 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984), as summarized recently by Hiller (1984), and evaluated by a WHO Committee (1983). Actual estimates (First, 1984; Hiller *et al.* 1982, 1985; Hinds *et al.*, 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984) imply a dosage to the passive smoker of less than 2 (range of 0.1 – 2) cigarettes/day, except in unusual circumstances; these estimates are ten- to one-hundred-fold less than that in the Repace and Lowrey model (1985). Dosage is the key ingredient to the question of association, and it will require further determination.

Epidemiology

Some have opined that involuntary cigarette smoke possibly contributes to the otherwise unexplained phenomena of lung cancer in nonsmokers and differences in lung cancer rates between rural and urban areas (Cooper *et al.* 1968; Hoegg, 1972), though most studies and reviews link this mortality to occupational and other environmental exposures (Cooper *et al.* 1968; Goldsmith and Friberg, 1977; Lippmann and Schlesinger, 1979; Shy *et al.*, 1978; U.S. Surgeon General, 1982).

At least in the United States, lung cancer deaths in nonsmokers have not increased in the last three decades in either sex (Garfinkel, 1981). Studies of the relationship between involuntary smoking and lung cancer have been performed primarily in females who are exposed to the sidestream smoke of their spouses. Females have lower lung cancer rates than males, even in smokers, and the relative risk ratios appear lower for female smokers than male smokers; these differences are thought to be due to differences in age of onset of smoking, of smoking habits, and occupational exposures (U.S. Surgeon General, 1980, p. 114). Although the occupational exposure of women along with their smoking may produce similar rates to those of males under similar circumstances, fewer women have such exposures (U.S. Surgeon General, 1980, p. 179). In general population samples, however, it is more difficult to accurately ascertain smoking and other exposures in women, especially in traditional societies.

Prospective Population Studies

In a recent study in Japan (Hirayama, 1981), nonsmoking wives of smoking husbands were claimed to have a higher risk of dying from lung cancer than nonsmoking wives of nonsmoking husbands. This study followed 91,540 nonsmoking wives age 40 and older for 14 yr (1966–1979). Husband's age (40–59, 60+) or occupation (agriculture or other) were used to standardize mortality rates for lung cancer and were compared depending on the smoking habits of the husbands; standardization was not on the wives ages or occupations. A relative risk ratio of 2 (1.90–2.36) in nonsmoking wives of heavy smoking husbands was found and was considered significant by the Mantel-extension chi two tailed test; it has not been resolved whether the statistical test was performed correctly. A re-analysis of the data (Harris and DuMouchel, 1981) used a chi-square test statistic for the disaggregated data. Estimating relative risk using maximum likelihood methods for the total set of data also yielded significantly higher rates in the nonsmoking wives with smoking husbands. However, in evaluating the disagregated data several inconsistencies and/or differences of small magnitude were found. For instance, for wives of husbands age 40 – 59 who work elsewhere, the rates for the nonsmoking husband group (10.0) and the rates for the ex- or light-smoking husbands (11.2) are not different; for husbands age 60 or more who work in agriculture, the rates for women with heavy-smoking husbands (35.7) are less than the rates for women with ex- or light-smoking husbands (43.8). As with wives of husbands age 40 – 59 who work elsewhere, wives whose husbands are age 60 or older who work elsewhere who are ex- or light-smokers have rates not distinguishably different from the wives of nonsmoking husbands of that age group or occupational group.

Further problems exist in evaluating the Japanese data, predominantly relating to the actual estimate of exposure to tobacco smoke and of other exposures in females. It may be difficult to correctly ascertain smoking habits of females in this traditional society, as smoking is considered improper for women. Furthermore, indoor exposures to indoor combustion products, especially charcoal or kerosene burning, is likely in Japanese society, and is probably greater in rural females.

Other exposures, either occupational, perri-occupational, ambient, and/or socially related are likely to have clouded the true differences amongst these women (Dore, 1967; Embree, 1939; Vogel, 1971). One Japanese study reported increased cancer related to heating and cooking fuels used especially in rural

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areas, as did one Chinese study (Leung, 1977); another Chinese study found no such effect (MacLennan *et al.*, 1977). It is difficult to ascertain how much time each group of women spends with their smoking or nonsmoking husbands. It is also difficult to determine the effects of ventilation in these homes on the exposure level; it may be that the women in the agriculture areas have homes with more ventilation as well as infiltration of pesticides and other substances. These problems persist because of other determinants of exposure, determinants of socioeconomic status, and the urban rural differences have not been characterized sufficiently, despite assumptions made about such differences (Hammond and Selikoff, 1981; Hirayama, 1981). Further, the major differences seen in wives of husbands age 40 to 59 in agriculture was based on only 3 female deaths in wives of nonsmoking husbands; further estimates of risk, depending on one's assumptions, could lead to different results (Rutsch, 1981).

Finally, other smoking-related causes of death were not significantly different between passive and nonpassive smoking wives. Subsequent letters to the editor of the *British Medical Journal* have been contradictory. Dosage estimates, as shown by the 1984 International Workshop, have been incorrect.

One study in the United States has been analyzed to determine the possible influence of husbands smoking on the mortaility experience of nonsmoking wives (Garfinkel, 1981). Adjusted lung cancer deaths among women with nonsmoking husbands matched with women with smoking husbands were not significantly higher in the first group than in the latter groups. The adjusted relative risk ratio for wives with husbands who smoked a pack or more per day was only 1.04. There is no serious disease in the women at the onset of this study. The relationship between the death certificate cause of death and that in the medical records in females was only 83%, indicating possible biases in this study and in other studies of mortality; this bias may be greater for females, as the death certificates and medical records match more closely for males. Only 41% of husbands' smoking was at home. The fact that mortality ratios for light smokers compared to nonsmokers is nearly 5 to 1 in the United States compared to 2 to 1 in Japan would indicate that one would be more likely to see the effects of involuntary smoking in the United States. However, it appears unlikely the wives with husbands who smoke heavily can have mortality ratios that approach those of regular cigarette smokers (Garfinkel, 1984). Thus, the Japanese study (and Greek study, below) may have possible biases in selection or in measurement (Garfinkel, 1984; Rylander, 1984). Garfinkel reported (1984) that their autopsy studies have indicated no atypical cells in the 47 nonsmokers studies. They are starting a new chohort study of 1.2 million people, in which more accurate exposure information will be obtained (Garfinkel, 1984).

Knoth *et al.* (1984) studied 59 females with bronchogenic carcinoma in Germany. The proportion who were nonsmoking spouses of smokers (61.5%) indicated a risk 3 times that based on smoking males. This indicates that there is a high likelihood of misclassification/bias in this study.

Gillis *et al.* (1984) have preliminary results from a cohort study of 16,000 in 2 urban communities in West Scotland. It was shown that cancer incidence and mortality may inconsistently be associated with some small but nonsignificant increase in risk in nonsmoking female spouses of smoking husbands.

There is a major problem in the phenomenological use of data on epidemiological Seventh Day Adventists (SDAs) in mathematical models (Repace and Lowrey, 1985). Generalizations based on SDAs are unjustified as they are a distinctly different group of individuals (compared to a random sample of the general population); they have different lifestyles in addition to different smoking habits. Epidemiologically, Repace and Lowrey (1985) use insufficient methods to control for differences in age and other confounding factors (Friedman *et al.*, 1983; Garfinkel, 1984; Roth, 1981; WHO, 1982; WHO/EURO, 1983).

As Rylander has indicated (1984), none of the cohort studies were designed to study this relationship. In fact, Friedman *et al.* (1983) showed the high rates of misclassification of smoking by spouses, which would over-estimate risk. Garfinkel (1984) has confirmed this misclassification bias. It is difficult to obtain complete information on passive smoking in nonsmoking women. An epidemiological study has to be designed specifically to measure their exposure as accurately as possible, and this is difficult to do. Furthermore, the long-term effects of passive smoking is difficult to establish because of the problems in classification and because of other exposures and/or previous exposures (such as in previously married women); marriage to a smoker is not equivalent to exposure, and other factors may mask important differences.

Case-Control Studies

Case-control studies are meant to measure relative risk (not true probability) and generate hypotheses (not definitive results).

Garfinkel (1984) reported on a recent attempt to do a case-control study. He indicated that half of the primary lung cancer cases were misdiagnosed (by histology) and half of the nonsmokers were current or exsmokers by their own report (Garfinkel, 1984). When this study was completed (Garfinkel *et al.* 1985), they had 134 cases, 90 with home exposure. Their relative risk ratio by the number of cigarettes the husband smoked in the home was 1.31 overall and over 2.0 for

more than 1 pack per day, both significant. Both are lower than that for light smokers.

Another case-control study (Sandler *et al.*, 1985) found no significant increase in lung cancer risk but found increases in non-tobacco-related cancers, that is, those normally used as positive controls for reasons of internal reliability and validity (i.e., the study is considered unreliable if the positive control shows an association and invalid if it is significant but the cases—lung cancer—are not). Other methodological and ascertainment problems might explain the gaffe.

A case-control study in Greece (Trichopoulos *et al.* 1981) compared spouses' smoking habits of female lung cancer patients with spouses' smoking habits of other female patients, after excluding smoking females. As indicated by the authors, having only 39 married nonsmoking females in the lung cancer group did not enable them to draw strong conclusions about their odd ratios. Furthermore, only about one-fourth of the lung cancer cases had histological conformation. The controls were matched on their occupation, age, education level, urban/rural residence, and duration of marriage, but were not matched on residence (*vis-à-vis* ambient exposures), other exposures, husband's occupation, or other factors of indoor exposure. It was noted that among the original set of female cases and female controls that the female cases smoked more, as expected, but the relative risk ratio of smoking cases appeared similar to the relative risk ratio of the nonsmoking married females with smoking spouses. These ratios were corrected in subsequent publications (Heller, 1983; Trichopoulos, 1984). Again the ascertainment bias of smoking in females in a somewhat traditional society is possible. The personal habits of the various groups of women are unknown, although others (Hammond and Selikoff, 1981) believe that they are such as to make the estimates of the differences conservative.

Other factors that would affect the exposure to the husband's smoking, such as ventilation in the home, and the time spent with the husband, is unavailable. Since this was a case control study with limited information about co-linear variables or intervening variables, it would take a prospective study in the community with better data collection to insure a better estimate of the probability of risk. Furthermore, such a study would avoid observer bias produced by using only one physician and the need to only one control group (Hammond and Selikoff, 1981). With a prospective study, there is a possibility of better histological conformation, including inclusion of adenocarcinomas which the investigators presently excluded; more recent investigations indicate that all four major histological types, including adenocarcinoma, are related to cigarette smoking (U.S. Surgeon General, 1980, p. 113).

Chan and Fung (1982) have reported on a hospital-based case-control study in Hong Kong. Comparing 83 female lung cancer cased to 139 females controls showed no difference in the proportions of each group with smoking husbands. Koo *et al.* (1985) performed a case control study in Hong Kong, in which the analysis of all histological types in never-smoking females did not reveal any significant increase in relative risk from passive smoking. Other environmental factors which encourage bronchial irritation are suspected. They found histological typing responsible for misclassification and biased risk values between active and passive smoking seen in other studies.

Correo *et al.* (1983) published a case-control study of lung cancer in nonsmoking men and women classified by the number of cigarettes smoked per day by their spouses. Relative risks in women was significant only for those with heavy (40+/day) smoking husbands. However, this study was based on 22 lung cancers in nonsmoking women and 8 in nonsmoking men. They examined whether or not there was an association with parents' smoking habit when they were children as well. No association was found with paternal smoking. There was an elevated risk in smokers whose mothers smoked, after controlling for other variables, but no elevated risk in nonsmokers. No attempts were made to ascertain *post hoc* bias in reporting, nor accuracy of the estimate of exposure.

Kabat and Wynder (1984) reported on 25 nonsmoking men and 53 nonsmoking women classified not only by whether or not their spouse smoked, but also whether or not they were exposed to smoke of others at work or at home. In women there was no increase in risk of lung cancer for any of these three measures. In men there was increased risk of lung cancer in those exposed at work (barely statistically significant), but no increase in risk in those exposed at home or from spouse's smoking. They concluded that more data must be collected before any conclusion can be drawn relating to the effects of passive smoking.

A study based on interviewing the next of kin of deceased cases (Miller, 1984) showed slightly higher rates of all cancer deaths in women with smoking husbands (versus those with nonsmoking husbands) but lower rates of coronary artery disease and other causes in those same women. The odds ratio was calculated incorrectly. Nevertheless, it showed significantly increased cancer deaths in only one of 4 age groups, and as low as 0.4 in another age group; the overall odds ratio was not significant. Examining only nonemployed wives reduced the significant odds ratio to nonsignificance (X^2 = 0.93), although the overall ratio was now significant; the latter still requires age adjustment before considered suggestive. Employed wives had an overall odd ratio of 0.8.

Models

Since estimated exposure in passive smokers is between 0.01–2 cigarette/day, one could linearily estimate an age adjusted relative cancer risk between

1.03–1.36. The impact of this on cancer incidence especially in the majority of the range, is considered small (Vutuc, 1983). The difficulty is that we do not know if the dose-response curve is linear (no threshold) or nonlinear (with a threshold), indicating that extrapolation at these low levels of exposure is risky.

The one-hit model of cancer risk is a crude model; it assumes a non-threshold linear dose-response relationship and extrapolation to low doses. As shown by others (Roth, 1981; Albert, 1981; Althshuler, 1981; Caplan *et al.*, 1983; Jacobi, 1984; Luken and Miller, 1977; Radford and St. Clair, 1984; Schnerderman, 1981; Task Force, 1982; Wyzga, 1981), this model overestimates risk from more likely exponential or mulihit models. The model and methods used by Repace and Lowrey (1985) and others do not provide estimates of precision, confidence intervals, or consistency estimates (Beran, 1971; Black, 1970; Luken and Miller, 1977; Smith, 1961), the very statistical bases of estimation procedures.

Discussion

The fundamental dilemmas are (1) basic epidemiological or statistical errors in previous studies which are often ignored by nonepidemiologists (U.S. Surgeon General, 1982, 1984); (2) misclassification of exposure and of lung cancer (Friedman *et al.*, 1983; Garfinkel, 1984); and (3) the problem of dose (Albert, 1983) and exposure-response relationships (Jarvis and Russell, 1984). The biological consequences of smoking require a certain dose over a certain time (Garfinkel, 1984; IARC, 1984; Vutuc, 1984), which if low, may not even be significantly noticed in low doses in large populations (U.S. Surgeon General, 1982). It seems unlikely that passive smoking is responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers (Repace and Lowrey, 1985). One must recognize also that nonsmokers may have developed lung cancer from other environmental agents: radon progency may account for 5%–30% (most likely 5%–15%) of such mortality (Edling *et al.*, 1984; Hess *et al.*, 1983: Jacobi, 1984; Radford and St. Clair, 1984), and volatile organic compounds (Albert, 1983; NRC, 1972), asbestos (Hirayama, 1981; Holland *et al.*, 1963), and various other environmental factors have been blamed as well. In conclusion, the Repace and Lowrey (1985) estimates of nonsmokers' lung cancer risk from passive smoking is an overstatement.

Lung cancer risk estimated to be twice as high in passive smokers as in nonsmokers not exposed to the smoke of their partner is hardly conceivable because of the absence of cell modifications in the tracheobronchial tract of passive smokers (Garfinkel, 1984). Thus, the problem of passive smoking may be too small to measure in population studies (Garfinkel, 1981; Rylander, 1984). A 1983 International workgroup (Rylander, 1984) agreed that there was sufficient association to support further research. Further case-referent approaches could be considered. Further research should measure actual exposure to environmental tobacco smoke, as recently requested by NCI (NCI RFA 84-Ca-14). It should consider the contributions of specific agents thought to produce cancer, such as nitrosamines and polycyclic hydrocarbons. Further research should include other possible carcinogenic agents and confounding factors, such as occupational exposure, other exposures of the nonsmoking household members, social status and other risk variables.

Conclusion

One must weigh several factors before we claim certain causality that smoking by parents, spouses, friends, and workmates will definitely give nonsmokers cancer. As previous public health experience has shown when one lacks causal links, anxiety increases, as do its sequaelae, as does cost, with increasing iatrogenic disease (i.e., induced by the ""healer") and little benefit in actually preventing overt disease, disability and premature mortality. **However, once causality has been shown, we must act quickly to prevent disease. In the interim, we should work to prevent active smoking.**

The U.S. Surgeon General's report 1982 (p. 249) stated: ""Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem." At present, it can only be concluded that it will require further investigation before the estimated probability of risk can be determined.

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LETTER TO THE EDITORS

Clark Johnson
Heinz Letzel, Munich, Germany

(Received 1 July 1985)

Dear Sir:

The article "A quantitative estimate of nonsmokers' lung cancer risk from passive smoking" by Repace and Lowrey (1985) concludes that 5,000 nonsmokers aged 35 yr or greater die every year in the United States of lung cancer as a result of exposure to tobacco smoke through passive inhalation. They model the exposure in two microenvironments: at home and at work. In an effort to determine the limitations of the methodology, we have re-examined their methods for estimating the exposure in the home. This seems to be justified, since they use the same strategy for both environments. This strategy can be summarized as follows:

1. Calculate the number of cigarettes smoked in the environment.
2. Use a theoretical model to translate this into a burden (uptake of particulate matter in mg per day).
3. Calculate the probability that a nonsmoker will receive this exposure.

Weaknesses on all three levels will be illustrated in this communication.

Inflated Estimate of Per-Person Cigarette Consumption

In paragraph 2 of Appendix A2 the authors assume that the average habitual smoker smokes 32 cigarettes/day. This rather high estimate of daily consumption was apparently abstracted from Repace and Lowrey (1980) in which they obtained a smoking rate per smoker-waking h of 2 cigarettes.

Hence, 32 cigarettes per day is calculated from an average rate of 2 cigarettes/h and 16 waking h/day. We prefer the estimate given in the 1980 National Health Interview: Survey Smoking Supplement of 21.7 cigarettes/day. If one corrects not only for this inflated estimate of cigarette consumption per day, but also for the incorrectly calculated percentages derived from Table A1 (33.75, 46.25, and 78.12% instead of 34.4, 45.9, and 81%, respectively), it can be calculated that 14.0 cigarettes are smoked by the average woman in the home, while 7.3 are smoked by the average man.

Inflated Estimates of Exposure

In the next paragraph the authors derive an estimate of the number of cigarettes smoked in the average U.S. home. Drawing on statistics generated by Bonham and Wilson (1981), they correctly indicate that 62% of U.S. homes *with children* contain one or more smokers and subsequently infer that of these homes (i.e., homes with smokers) 40% have two smokers, while in 33.5% the husband smokes, and 26.5% the wife smokes. Using these figures and the total number of cigarettes smoked at home as a basis, they calculate that 22 cigarettes/day are "estimated to be smoked daily in the average U.S. home." This estimate, if it is valid at all, can only be applied to homes with children, where one or more smokers are present. This can, by no means, be regarded as the average U.S. home. Using our baseline smoking rate the value is 14.6.

They subsequently assume that everyone of these cigarettes exposes a nonsmoking adult. This assumption implies that the housewife is always accompanied, and that, in the case where both husband and wife smoke, a third adult lives in the home. This assumption is by no means a conservative one.

It seems, however, that a method could be devised by which a more realistic estimate of household exposure in cigarettes per day could be calculated. If, for example, one attempts to calculate the number of cigarettes smoked in the home, which have the poten-

tial of exposing a second adult, one is led to the following calculation

$$0.40 \times 0 + 0.265 \times 7.3 + 0.335 \times 7.3 = 4.4$$

40% of the homes, containing at least one smoker, contain in fact two smokers. These adults cannot be regarded as being primarily exposed through one another's smoking habit (i.e., 0.40×0). Similarly, if only one adult smokes, then the only time that their smoking can expose the other adult is at those points in time when they are both occupying the house. Hence, the 33.75% of the waking day spent in the home by the man is the limiting factor. We calculate that 7.3 cigarettes are consumed in these 5.4 h (i.e., 0.265×7.3 for women, 0.335×7.3 for men). Only 4.4 (30%) of the 14.6 cigarettes smoked at home can reasonably be attributed to exposure of nonsmoking adults.

Doubtful Theoretical Model not Clearly Applicable

The authors culminate their derivation by estimating the average exposure to particulate matter in mg/day for an adult nonsmoker. The equation used was originally published by the authors in 1980 (Repace and Lowrey, 1980).

In that article it is clear that the derivation of this formula depends upon two important simplifications of the smoking process:

1. Smoking as a statistical process.

In deriving the model, the authors assume "that smoking is a random process when it occurs among large groups." The authors, however, use the model in situations in which only a single smoker is present (i.e., the home), hardly one that can be regarded as characteristic of large group phenomenon.

2. Pollution equivalent to steady state levels.

A single smoker in a small room may produce a relatively constant level of pollution. The authors, however, assume that this constant level is equivalent to a theoretically derived "steady state", an assumption that has not been substantiated.

The application of this formula may be appropriate. However, it is incumbent upon the authors to offer the reader a demonstration of the fact that the assumptions, upon which it is based, can be massively violated without loss of validity.

Questionable Choices With Regard to Application of the Formula

Even if the equation is theoretically correct, which we doubt, it is incorrectly applied. As stated earlier, there is simply no basis to assume that an adult nonsmoker will be exposed for every hour of the waking day in every home where cigarette smoking takes place. Consequently, the authors' assumption that, if an adult is exposed, he or she will be exposed 16 h every day, is a dramatic inflation of an already inflated estimating procedure. From our calculations, a value of 5.4 h would more likely be appropriate.

Finally, the authors suggest that the probability of exposure is 62% for an adult nonsmoker. As reported earlier, this does not seem to be a correct estimate. Not only does it fail to account for the possibility that there are single parents, but it also includes as exposed those homes in which both parents smoke. Since we have no data for the percentage of single parents in the U.S. population, we will assume that this effect balances the number of times that a third adult actually is present in the home, where both parents smoke. Still, since 38% of the surveyed homes had no smokers, and 25% had two or more smokers, it seems far more reasonable to assume that the probability of exposure is 37% (100% − 38% − 25%).

Conclusion

Our examination has shown that the figures derived by the authors are based upon incorrect theoretical assumptions and inflated empirical estimates. The other calculations, contained in their paper, suggest to us that the tendency to choose inflated estimates with regard to exposure in the home was consistantly followed. As a result, one must conclude that the estimate of 5,000 lung cancer deaths per year in the United States, due to exposure to ambient tobacco smoke, does not represent an accurate assessment of the problem.

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HEALTH RISKS OF PASSIVE SMOKING: PROBLEMS OF INTERPRETATION

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Introduction

It is notoriously difficult to draw sound conclusions about causation from epidemiologic studies of associations. In his *Principles of Medical Statistics*, Sir Austin Bradford Hill, one of the founders of modern epidemiology, warns in connexion with positive associations: "Merely to presume that the relationship is one of cause and effect is fatally easy; to secure satisfactory proof or disproof, if it be possible at all, is often a task of very great complexity" (Hill, 1949).

The fundamental difficulty in conventional case-control and prospective surveys relates to the comparability of cases and controls. Thus, when we compare the incidence of lung cancer in smokers with that in nonsmoking controls we determine an association which, in the great majority of studies (U.S. Surgeon General, 1982), has been found to be positive. But, as we have been told *ad nauseam*, "association does not necessarily imply causation." Smokers and nonsmokers are generally self-selected and we need to be assured of the strict comparability of the two groups—in every pertinent respect except smoking—before inferring causation from association (Fisher, 1959; Yerushalmy, 1971). An analogous issue arises in connexion with various studies of passive smoking (Burch, 1981a): are persons married to smokers comparable, on the average, in all other pertinent respects to persons married to nonsmokers? Alas, the phenomenon of assortative mating is well established and accordingly we are not at liberty to assume that studies of any disease, in relation to the smoking status of the spouse or other household members, comply with the scientific requirements for valid inferences about cause. The nonsmoker who marries a smoker is unlikely to be representative of all nonsmokers.

My main purpose here is to examine Repace and Lowrey's (1985) arguments about lung cancer from the methodologic viewpoint.

Outline of Repace and Lowrey's Procedure

1. Exposure of nonsmokers

From measurements of the concentration of respirable particles between 0.01 and 3.0 μm diameter in representative samples of room air, and from surveys of lifestyles, Repace and Lowrey (1985) estimate the total exposures of nonsmokers (range and average) in terms of mg cigarette tar per day.

2. Epidemiologic studies of lung cancer in passive smokers

They review 13 epidemiologic studies of lung cancer risk in the nonsmoking spouses of cigarette smokers. In 12 of these, the only index of exposure was the strength of the spouse's smoking habit. The mortality ratio for persons married to smoking spouses versus those married to nonsmokers, clusters around a value of 2.0.

They also compare the sex- and age-adjusted mortality from lung cancer in Seventh Day Adventists (SDA) self-reported nonsmokers with that in never-smokers in the general U.S. population. Non-SDA never-smokers had an average standardized death rate from lung cancer that was 2.4 times that of SDA never-smokers. This latter group, they believe, was less likely to be exposed to ambient tobacco smoke than the former.

3. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking

Repace and Lowrey (1985) assume that the mortality ratio (2.4) derived from the SDA study implies causation and thereby calculate that some 4,700 lung cancer deaths per year have been caused among U.S. nonsmokers owing to passive smoking. They conclude that this figure agrees well (within 10%) with

Hirayama's (1981) estimate of mortality from lung cancer attributable to passive smoking by the nonsmoking wives of Japanese smokers.

4. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of active smokers

From many studies of lung cancer in active cigarette smokers reviewed by the U.S. Surgeon General (1982), and a linear exposure-response relationship, Repace and Lowrey derive an alternative estimate of the lung cancer death rate in the U.S. resulting from passive smoking. This procedure leads to an estimated 555 lung cancer deaths per year, nearly one order of magnitude lower than the rate (4700 per year) calculated under procedure 3 above.

5. Discussion of discrepancy between procedures 3 and 4

Repace and Lowrey speculate upon ways in which the lower estimate might be raised to the upper value.

Critique

Each of the above stages in Repace and Lowrey's procedure is discussed in turn.

1. Comment on: Exposure of nonsmokers

To make a valid estimate of the effective exposure of passive smokers to carcinogens we require the following information at least: (i) the nature of the carcinogens and their concentration in sidestream smoke particles; (ii) the anatomical location of the target cells; (iii) appropriate parameters of exposure such as the time-concentration and/or integral dose of carcinogens at the cells at risk; and (iv) an established model of tobacco smoke carcinogenesis incorporating factors for the sex- and age-dependence, dose and dose-rate effects, genetic susceptibility, etc..

Having little or no definitive guidance under any of these requirements, current estimates of effective exposure to carcinogens should be regarded as conjectural. Nevertheless, for the purpose of comparing passive smoking with active smoking, we have at present little option but to use the kind of data given in Repace and Lowrey's Table 1, although, according to Jarvis and Russell (1984), measurements of cotinine concentrations in urine samples are preferable.

2. Comment on: Epidemiologic studies of lung cancer in passive smokers

In addition to problems concerning occupational hazards, the choice of controls, etc., the reviewed epidemiologic studies are vulnerable to one elementary as well as a fundamental objection. To take the elementary objection first, Repace and Lowrey's Table 1 gives an estimated average daily exposure of nonsmokers in the home only, of 0.10 mg, and at work only, of 0.44 mg. It follows that studies of cancer and lung cancer risk in passive (or active) smokers, in relation to the smoking status of the spouse and household members, provide wholly inadequate evidence for association with actual exposure. Average total exposure appears from Repace and Lowrey's calculations to be dominated by the workplace component. This view is borne out in the Japanese environment by actual measurements of cotinine concentrations in urine samples from 167 male and 305 female nonsmokers (Matsukura *et al.*, 1984). Using Duncan's multiple-range test for several comparisons the authors found no significant difference between persons (200) not exposed at home, who had an average concentration of 0.51 $\pm$0.09 μg/mg creatinine, and those (272) exposed at home who had an average of 0.79 $\pm$0.10 μg/mg creatinine. Consequently, the relatively large differences in cancer risk between persons with smoking spouses, and those with nonsmoking spouses, are most unlikely to be due to differences in the levels of passive smoking, which on the average are small.

Only one study, that of Kabat and Wynder (1984), took account of exposure of nonsmokers in the workplace. That survey disclosed 6 male cases and 5 controls exposed in the home but 18 (out of 25) cases and 11 (out of 25) controls exposed at work ($P = 0.05$, ignoring the problem of multiple tests). With respect to women, Kabat and Wynder (1984) report: ". . . 16 of 53 cases were exposed at home compared to 17 of 53 controls, and 26 of 53 cases were exposed at work compared to 31 of 53 controls." Thus no significant differences were found in the data for women but the trend favours a prophylactic rather than a causal hypothesis.

The fundamental objection to all the reviewed studies of passive smoking concerns, of course, the lack of established comparability between the exposed and the nonexposed groups. This objection applies equally to studies of cancer risk in relation to the spouse's and household smoking, and to the comparison between SDA and non-SDA never-smokers. Seventh Day Adventists differ from never-smokers in the general U.S. population with respect to various features of lifestyle. Moreover, they are not drawn randomly from the general population; they are either self-selected and/or born of self-selected parents.

Hence, no reliable inferences about cause can be drawn from associations determined from either of the above types of evidence. In the absence of randomization we can have no confidence that hidden variables, particularly of a constitutional character, are not responsible for the observed associations.

By an interesting irony one of the studies of passive smoking (Sandler, *et al.*, 1985a, 1985b), if taken at face value, provides a fair refutation of the hypothesis

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that the association with the risk of cancer is causal (Burch, 1985). Sandler *et al.* (1985a) studied the overall cancer risk in active and nonsmokers in relation to the number of household members who smoke. The odds ratio was normalized to unity for households with no (other) members who smoked. For households with one (other) smoking member the odds ratios are 1.42 for active smokers and 1.45 for nonsmokers; for households with two (other) smokers the corresponding ratios are 2.25 and 2.32; and for three or more, the ratios are 2.42 and 2.75. Within the error limits the ratios for active smokers are identical with those for nonsmokers. Treating them as identical, Burch demonstrated that if A represents the carcinogenic effect of active smoking and P the carcinogenic effect of passive smoking resulting from one household smoker then, for either additive or multiplicative (interactive) models of carcinogenesis, $A + P = 0$ (Burch, 1985). This relation has three possible solutions: (i) active and passive smoking are both noncarcinogenic ($A = P = 0$); (ii) active smoking is carcinogenic and passive smoking is prophylactic ($A = -P$); and (iii) active smoking is prophylactic and passive smoking is carcinogenic ($P = -A$). Burch added: "The statistical uncertainty in Sandler's Table 1 is large enough to permit slightly less paradoxical inferences . . ."

Sandler *et al.* (1985b) replied to this analysis giving a further breakdown of their data showing odds ratios for the overall cancer risk in active and in nonsmokers in relation to household exposure to cigarette smoke during childhood only, adulthood only, and both periods of life. These supplementary data only deepen the paradox: Consider the simple additive model and define N as the average risk per person of cancer from all causes unconnected with smoking; A is the average additional risk from active smoking, including the smoker's exposure to the associated ambient cigarette smoke; P_c is the additional average risk from exposure to household cigarette smoke during childhood only; and P_A is the corresponding risk from exposure to household cigarette smoke during adulthood only. (The study population was aged from 15 to 59 yr and I assume these risks are substantially less than unity.) For nonsmokers exposed to household cigarette smoke during childhood only, with total risk $N + P_c$, we require from the Table of Sandler *et al.* (1985b): $(N + P_c)/N \cong$ the odds ratio, 1.3, giving $P_c \cong 0.3N$, a nonparadoxical result. For active smokers who were exposed to household cigarette smoke during childhood only, we have: $(N + A + P_c)/(N + A) \cong 1.9$. Substituting for P_c, we obtain $A \cong -0.7N$, a highly paradoxical result implying that active smoking in conjunction with passive exposure to household cigarette smoke during childhood only, is markedly prophylactic! A similar conclusion emerges from the multiplicative model.

However, when we consider the odds ratios for exposure to household cigarette smoke during adulthood only, we obtain $A \cong 3N$, which for the overall cancer risk in both sexes is substantially larger than directly observed associations (U.S. Surgeon General, 1982). Furthermore, although it is logically acceptable that active smoking in conjunction with passive smoking during childhood only is prophylactic, but in conjunction with passive smoking during adulthood only it is carcinogenic, the sharp reversal of effect between childhood and adult phases imposes a severe strain on biological models of carcinogenesis.

The "solution" to these findings of Sandler *et al.* (1985a, 1985b) that minimises paradox is, in effect, the original one: $A = P_c = P_A = 0$; with the odds ratios being attributed to selection effects arising from assortative mating.

3. *Comment on: Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking*

Even if we adopt the hypothesis that passive smoking causes lung cancer and ignore selection problems, the evaluation of the epidemiologic studies for the purpose of risk calculations still poses severe problems. We have no direct measure of the relevant exposure to ambient cigarette smoke in any of the studies of associations. Although it is plausible to suppose that SDA nonsmokers have a lower exposure to ambient cigarette smoke than non-SDA never-smokers, we have no direct measure of the average levels in either group.

For these reasons alone the calculation by Repace and Lowrey of the number of lung cancer deaths (LCDs) per year in the United States caused by passive smoking must be regarded with the utmost suspicion. Associations determined from conventional case-control or prospective nonrandomized surveys should play no part in a scientific estimate of the magnitude of risks.

4. *Comment on: Estimated death-rates from lung cancer in nonsmokers using epidemiologic studies*

From the Surgeon General's estimate that 85% of all lung cancers are due to smoking and a linear exposure-response relation, Repace and Lowrey calculate that about 555 LCDs are caused in the United States each year through nonsmokers being exposed to ambient tobacco smoke. Elsewhere I have reviewed the methods used in the U.S. Surgeon General's (1982) report on cancer and, in particular, the arguments about lung cancer (Burch, 1983). If Lilienfeld's (1983) invited response to my many criticisms may be regarded as the best available defence of the Surgeon General's methods then I hope that I might be forgiven for suggesting that we need give little credence to them (Burch, 1984).

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To quote from my summary (Burch 1983): "Part II of the [Surgeon General's] Report describes the five criteria for causality that have guided the judgment of committees since 1964. I show that not one of the criteria, plausibly interpreted, is satisfied by the epidemiologic evidence for lung cancer." Lilienfeld (1983) was unable to demonstrate the contrary and to all my pointed enquiries he did not supply a single answer. On the Surgeon General's own criteria the hypothesis that the association between smoking and lung cancer is entirely causal in origin should be rejected.

My main attack, however, was launched at a more fundamental level: "The five criteria and the subjective method of 'judgment' are inappropriate to a scientific analysis; they should be replaced by the objective testing of hypotheses." Given a genuine association between a habit, *H*, such as cigarette smoking, and a cancer, *C*, such as lung cancer, we are obliged to consider all the following possibilities: (i) *H*, or something closely connected with it, such as the means of ignition, causes *C*; (ii) *C*, or a connected pre-*C* condition, causes *H* (I call this the "converse causal" hypothesis); (iii) a "third" factor causes, or predisposes to, both *H* and *C*; and (iv) because (i) to (iii) are not mutually exclusive any combination of them might be needed to account for an established association.

A comprehensive evaluation of an association requires an assessment of the relative contributions of (i), (ii) and (iii) complete with confidence limits. I had to admit: "My own attempts to derive the magnitude of the causal component of the association between smoking and lung cancer have been unsuccessful; errors of diagnosis and death-certification alone are apt to defeat such efforts." We are fortunate that other investigations—see below—help us to arrive at a "best estimate" of this causal component.

5. Comment on: Discussion of discrepancy between procedures 3 and 4

On encountering a near order of magnitude discrepancy between alternative estimates, most investigators would express dismay; it is to the credit of Repace and Lowrey that they display no outward signs of disappointment. Nevertheless, their ". . . discussion of alternative exposure-response relationships" has one conspicuous feature. Means are sought only to raise the lower estimate of 555 LCDs per year to the higher (4700 LCDs per year) and none in the reverse direction. I suggest that as little faith should be vested in the one estimate as in the other; both incorporate the same fundamental fallacy of arguing from association to causation.

It is widely, one hopes universally, recognized that the best way of eliminating most forms of bias, both in therapeutic trials and in epidemiologic studies of causation, is through randomization. Feinstein (1985) describes the randomized trial as the definitive "gold" standard in epidemiology. In the only practical form of such trials so far exploited in connection with the effects of active smoking, persons satisfying defined entry criteria were allocated randomly to one of two groups: (a) the intervention group which was subjected to intensive advice on the part of the investigators to quit smoking; or (b) the usual care, control group, which received no such advice. Levels of smoking were then monitored in both groups and after a suitable period the outcome, mainly in terms of mortality from various diseases and all causes, was assessed for the two groups.

Two such randomized trials have been carried out in which the findings for lung cancer have been reported: the Whitehall Study in London, England (Rose *et al.*, 1982) with a 10-yr follow-up; and the Multiple Risk Factor Intervention Trial (MRFIT, 1982) in the United States with a 7-yr follow-up. Although this latter trial cost some $120 million and, aiming at a reduction of heart disease, included dietary advice and stepped care treatment for hypertension in the intervention group—as well as antismoking advice—the results have not achieved prominence in the medical literature. They are not even mentioned by Repace and Lowrey. It is remarkable that reputable trials that cost so much should be valued so little.

Substantial reductions in smoking were achieved through the efforts of the investigators in the intervention groups, over and above the unplanned reductions in the usual care, control groups. By combining deaths and registrations for lung cancer in the Whitehall Study with deaths from lung cancer in the MRFIT (registrations not being reported in that study) we maximize numbers and obtain the best available direct epidemiologic test of the efficacy of reducing or quitting cigarette smoking. In the combined intervention, low-smoking groups, some 56 cases of lung cancer were recorded out of 7,142 men at entry (0.78%); in the usual care, relatively high-smoking groups, 53 cases were found out of 7,169 at entry (0.74%). The small advantage enjoyed by the high-smoking groups is, of course, not statistically significant; but it is strikingly consistent with the hypothesis that the association of active smoking with lung cancer has little or no causal component.

Because Sandler *et al.* (1985a, 1985b) studied all types of cancer, the outcome of the randomized trials for all cancers other than lung cancer are also of special interest. Some 88 cases (1.23%) were recorded in the combined low-smoking intervention groups but only 60 cases (0.84%) in the more heavily smoking usual care groups! It would be interesting to know whether a detailed statistical analysis of these combined results would reject the null hypothesis, as it did in the Whitehall Study at the level $P = 0.003$ (Rose *et al.*, 1982).

One possible weakness of this type of intervention trial must be mentioned. Quitting smoking might be followed by psychological stress, or other changes in lifestyle, that are carcinogenic. Rose *et al.* (1982) observed only "minor" psychological effects of intervention but believe that further study is needed to test the hypothesis that quitting smoking has adverse effects on the cancer risk.

Before concluding the review of these randomized trials the findings for deaths from all causes should be quoted because they yield the largest numbers and have some claim to be the most important. In the combined intervention groups, 388 deaths in 7,142 were reported (5.43%); and in the more heavily smoking control groups, 388 deaths in 7,169, or 5.41%, were reported. (It should be remembered that in the MRFIT study the intervention group also received dietary advice and treatment for hypertension.) Suffice it to say that a reduction in overall mortality does not appear to be among the benefits of quitting smoking.

This is not an isolated finding; it corroborates an earlier analysis (Burch, 1981b) that was also designed to defeat the bias of self-selection and was exempt from the problems connected with intensive intervention. To avoid the errors of certification of the cause of death I analysed the temporal trends in sex- and age-specific mortality from all causes in England and Wales, over the period 1950 to 1976. These trends were compared, for various latent periods, with the corresponding temporal trends in sex- and age-specific rates of cigarette consumption (on a "constant tar" basis), which rose during the early part of the period surveyed and fell during the latter part. The fall in death rates was greater during the rise in cigarette consumption than during its fall. Differences in the age-pattern of mortality between the early and late periods showed that, up to the age of about 45 yr, the fall in overall mortality was almost entirely accounted for by the near eradication of tuberculosis. No causal effects of smoking on overall mortality could be discerned although, if the associations observed in case-control and prospective studies had a causal basis, they should have been readily detected.

Conclusions

When the most reputable of direct epidemiologic studies, randomized controlled intervention trials, fail to demonstrate any of the benefits widely expected from quitting active smoking, it is not surprising that Repace and Lowrey's alternative estimates of the effects of passive smoking on the incidence of lung cancer—both based on spurious arguments—should differ by almost an order of magnitude. The conclusion that exposure to ambient tobacco smoke produces ". . . about 5000 lung cancer deaths per year in U.S. nonsmokers aged > 35 years . . ." belongs more to speculation than reality. When we take into account the outcome of the randomized trials together with the paradoxical implications of the findings of Sandler *et al.* (1985a, 1985b), the best estimate of LCDs per year is approximately zero.

No methodologically sound investigation of putative carcinogenic effects of passive smoking has yet been carried out. In the light of the size and cost of the randomized trials of the effects of quitting smoking—and of the disappointing results—it must be doubted whether any methodologically sound study of the requisite sensitivity will be undertaken in connexion with passive smoking in the foreseeable future.

Repace and Lowrey may feel justified in—and can hardly be blamed for—following practices that, in spite of numerous warnings (Hill, 1949; Fisher, 1959; Brownlee, 1965; Yerushalmy, 1971; Feinstein, 1979) are still commonplace in epidemiology. In the words of a distinguished clinical epidemiologist, a "licensed" epidemiologist ". . . can obtain and manipulate the data in diverse ways that are sanctioned not by the delineated standards of science, but by the traditional practice of epidemiologists" (Feinstein, 1979). We must hope that, before further public alarm is generated, wiser and more scientific counsels will prevail.

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LETTER TO THE EDITORS

Introduction

Repace and Lowrey (1985) estimate exposure to environmental tobacco smoke (ETS) in Appendix A. In Appendix B they extrapolate an exponential dose response curve to the number of lung cancer deaths presumed to be caused by passive smoking in the community. In Appendix C they contrast lung cancer mortality in nonsmokers, comparing Seventh Day Adventists (SDAs) with a group of non-SDAs and then, assuming this difference to be caused solely by passive smoking, extrapolate the putative effect of passive smoking to the U.S. population to estimate the decrease in life expectancy presumed to be due to ETS.

In the following, I express the difficulties I have in accepting these estimates.

Appendix A

With regard to environmental tobacco smoke, I question whether "the daily exposure of individuals can be estimated" accuratedly using global statistics as described in appendix A. By definition, exposure occurs to a nonsmoker in the presence of an active smoker. Couples or groups containing at least one nonsmoker and one person smoking are the appropriate statistical units, not the individual! Such groups are dynamic, especially at the worksite. In general, smokers mix with smokers and nonsmokers with nonsmokers. Thus, office workers often control their own microenvironment. Likewise, at home, couples tend to be or to become alike in their smoking behavior. Consequently, it is quite difficult to estimate the typical nonsmoker's exposure to ETS accurately. It can be shown that the estimates given in this paper are overestimates, caused by the authors' disregard of the grouping of smokers and nonsmokers.

Consider, for example, the derivation of exposure in the home (exposure at the worksite is much more dynamic and variable from site to site). In Appendix A2 Repace and Lowrey consider adult couples in which the husband works and in which 42% of the wives are also employed. From their sources, only 37% of these couples have a nonsmoker exposed to ETS. Assuming that exposure requires contemporaneous occupation of the same space, it follows that these couples are together, at most, 34% of the waking day (the time given for the husband to be at home). Irrespective of which partner smokes the 32 cigarettes per day (cpd) assumed for a typical smoker, the nonsmoker is exposed at home to, *at most*, $32 \times 0.34 = 11$ cpd and this occurs in 37% of all two-person homes. Repace and Lowrey estimate the exposure to be 22 cpd in 62% of homes!

Now, consider Appendix A1 in which the exposure at the worksite is estimated. At no point in their argument do the authors consider the aggregation of smokers with smokers and nonsmokers with nonsmokers. Instead they assume a perfect mixing of smokers and nonsmokers in deriving their estimates. If, on the other hand, all smokers worked with smokers and nonsmokers with nonsmokers, then the global statistics they use would still describe the population but there would be zero exposure to ETS! Repace and Lowrey's estimates can only therefore be taken as an upper boundary to the upper limit of exposure to ETS.

Their method of estimation may also be criticised on theoretical grounds. Here and elsewhere in the paper the authors multiply averages and assume that the resultant product is the average of the convolution of the two original statistical distributions. This is true only if the two variates are independent. If not, then

$$E(xy) = E(x) \cdot E(y) + \rho\sigma_x\sigma_y,$$

where ρ is the correlation coefficient of x and y, σ the standard deviation, and E is the expectation or average. It is likely that the variate, air exchange rate is positively correlated with both density of occupation and with respiration rate, and that duration of exposure is negatively correlated with density of occupation and with respiration rate. The combined effect of these associations are unknown.

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Appendix B

In Appendix B, the model is given as

$$P(D) = 1 - \exp(bD),$$

where D is the exposure, b is a constant, and $P(D)$ is the risk of a lung cancer death. The use of this model may be criticised on the following grounds:

- the relationship of passive smoking with lung cancer has *not* been shown to be a cause and effect relationship so that such modelling is, at best, premature;
- "the assumption of a no-threshold effect for carcinogens is also unproved" (Abelson, 1984);
- "the ambient measurements may have little or no bearing on the amounts that actually reach the target tissue" (Doll, 1985).

Thus, it is unlikely that such a simple model will adequately describe a complex process of carcinogenesis. A more general approach recognizes that tumor response is a function of delivered dose, D^* and that D^* is a *nonlinear* function of D, the exposure. Thus, the one-hit model

$$P = 1 - \exp(-[a + bD])$$

is a special case of this relationship (Hoel *et al.*, 1983) where D has been substituted for D^*. Hoel *et al.* (1983) give scenarios in which the 'standard approach,' extrapolated below the range of observed values underestimates the dose required for a given tumor incidence by factors of 50 to 100. The "hockey stick" relationship for carcinogens whose metabolites form DNA adducts can easily be taken for a straight line relationship if the minimum observed exposure is above the curve on the "hockey stick" (Hoel *et al.*, 1983). In a comparable situation to environmental tobacco smoke, the delivered dose/administered dose of formaldehyde in ambient air was shown to be significantly nonlinear (Casanova-Schmitz *et al.*, 1984). Starr and Buck (1984) show that four common dose-response models, the probit, logit, Weibull and multistage, all fitted the observed data on cancer risk from formaldehyde inhalation and could not therefore be discriminated among on the grounds of goodness of fit. Assuming that these models can be compared in fitting both administered and delivered dose curves, Starr and Buck (1984) show that, in all models the use of delivered dose gave lower estimates and lower upper confidence limits of cancer risk for a given low administered dose. More important, the range of the upper confidence limits increased among models as the administered dose fell.

In the above two studies the examples are based on animal exposures with zero tumors at zero dose. The one-hit model used by Repace and Lowery likewise has a zero intercept term. This is equivalent to assuming that the mortality rate of lung cancer is zero in the absence of ETS. Thus, yet again, Repace and Lowrey assume ETS to be the sole cause of lung cancer in the nonsmoker!

Appendix C

Here, Repace and Lowrey (1985) use unpublished data on lung cancer deaths (LCDs) in two groups of nonsmokers, followed roughly for the same period. If we accept that biases in ascertainment, classification and recording of LCDs are comparable in these two groups of SDAs and non-SDAs, then what? As before, Repace and Lowrey (1985) ascribe this difference soley to differences in exposure to environmental tobacco smoke (ETS). We are not, however, given the death rates from other causes of death in these two groups. If the death rates for motor vehicle accidents differ in the two groups, would Repace and Lowrey ascribe this difference likewise to differences in ETS? Again if mortality from cancer of the reproductive system is higher in SDA women than in non-SDA nonsmokers, would Repace and Lowrey assume that passive smoking had a protective effect?

In an editorial comment on a prospective study over a 20-yr period, the conclusion is questioned that eating fish is beneficial to health, although a lower mortality from heart disease is demonstrated. The editor points out that fish consumption may be associated with higher rates from other causes of death (Glomset, 1985). A similar problem exists with this method of estimation.

Conclusion

In some situations, a case can be made for reversing the usual definitions of the null and alternative hypotheses (Anderson and Hauck, 1983). This, however, is *not one of them*. The null hypothesis that passive smoking and lung cancer mortality are causally unrelated still stands. Until it is rejected, I consider it irresponsible to apply risk management techniques, even if they had been applied correctly.

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Lung cancer and passive smoking: predicted effects from a mathematical model for cigarette smoking and lung cancer

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Summary Epidemiological studies of active smokers have shown that the duration of smoking has a much greater effect on lung cancer risk than the amount smoked. This observation suggests that passive smoking might be much more harmful than would be predicted from measures of the level of exposure alone, as it is often of very long duration frequently beginning in early childhood. In this paper we have investigated this using a multistage model with five stages. The model is shown to provide an excellent fit to data on the incidence of lung cancer among smokers, ex-smokers and non-smokers in a cohort of male British doctors. Contrary to our expectation the model predicted only a slight increase in relative risk with increasing duration of passive exposure. Allowing for exposures early in life does not therefore explain the discrepancy between the relative risk of about 1.5 calculated from epidemiological studies of lung cancer and the low levels of exposure indicated by cotinine measurements in those passively exposed.

It has been suggested, using data from epidemiological studies of lung cancer and passive smoking (i.e. exposure to other people's tobacco smoke), that the relative risk of lung cancer among non-smokers living with smokers, compared to non-smokers living with non-smokers is about 1.5 (see, for example, Wald *et al.*, 1986). This estimate of relative risk is considerably higher than one would predict on the basis of studies of cotinine levels in non-smokers living with smokers (Committee on Passive Smoking, 1986). It is clear that epidemiological studies of passive smoking are particularly difficult to carry out because of the large errors inherent in obtaining adequate histories of such past exposure and because the studies need to avoid even slight biases as the relative risks involved are small.

Epidemiological studies of active smokers have however shown that the duration of smoking has a much greater effect on lung cancer risk than the amount smoked. For example heavy smokers (30 cigarettes per day) of 15 years duration have been shown to have only about one tenth the excess lung cancer risk of moderate smokers (15 cigarettes per day) who have smoked for 30 years, although the total number of cigarettes smoked is the same (Peto & Doll, 1984). This observation suggests that exposure to tobacco smoke at the low levels incurred during passive smoking might be much more harmful than would be predicted from measures of the level of the exposure alone, as passive exposure is often of very long duration frequently beginning in early childhood.

In this paper we have investigated the possible effects of such long duration exposure to passive smoking starting in childhood by modelling the effect of cigarette smoke on lung cancer incidence using a multistage model, and compared the estimates so obtained to those observed in epidemiological studies.

A multistage model for lung cancer

The model

The idea that a cancer is generated only after a cell has undergone a series of distinct ordered transformations or 'stages' was introduced to explain the observation that the mortality rates for many sites of cancer that are epithelial in origin increase as the fourth, fifth, or sixth power of age.

Multistage models have also been highly successful in describing many features of experimental carcinogenesis, for a review see Peto (1977) or Day (1983). The model as proposed originally by Armitage & Doll (1961) is the best known formulation and a brief description of it is given in the **Appendix**. In this formulation, if there are k stages involved for the cancer in question (normal cell = stage '0', stage 1, ..., stage k = cancer cell), we denote the probability that a cell which is at stage $i-1$ transforms into stage i in unit time as a_i, $i=1, \ldots, k$. According to this model, if these a_i remain constant throughout life, and if the time for a fully transformed malignant cell to grow into a clinically detectable tumour is ignored, then the incidence rate at age t will be proportional to t^{k-1}. It follows that if the logarithm of the age-specific incidence rates are plotted against the logarithm of age, then the plotted points will fall on a straight line with slope $k-1$.

Data on the incidence of lung cancer in non-smoking US males have been published by Kahn (1966) and Hammond (1966), and together include 127 cases of lung cancer. The data have been combined by Doll (1971) and are reproduced in Figure 1. It can be seen that they lie very close to a straight line with slope four, indicating that five stages are appropriate in the model for lung cancer. Among regular cigarette smokers the incidence rises more rapidly with age, and the slope of the line is about seven, but when the rates are plotted against duration of smoking, rather than age, the incidence again rises approximately as the fourth power, see Figure 1 (Doll, 1971).

In order to understand which stages in the multistage model are affected by smoking, it is necessary to consider the following two critical epidemiological observations. Firstly the fact that age at starting to smoke and duration of smoking are critical determinants of lung cancer risk, and secondly the fact that after stopping smoking the incidence rate remains approximately at the level when smoking stopped (Doll & Peto, 1976). In terms of the multistage model, these can be shown to imply that cigarette smoke has a strong effect on an early stage, probably the first, and also that it affects a late stage, but not the last (Doll, 1978; Day & Brown, 1980). When attention is restricted to smokers of cigarettes only, who also have a record of unchanging smoking habits, the relation between lung cancer incidence and number of cigarettes smoked per day is greater than linear, see Figure 2, and this provides additional evidence that more than one stage in the process is affected (Doll & Peto, 1978).

In the present paper we first show that a multistage model

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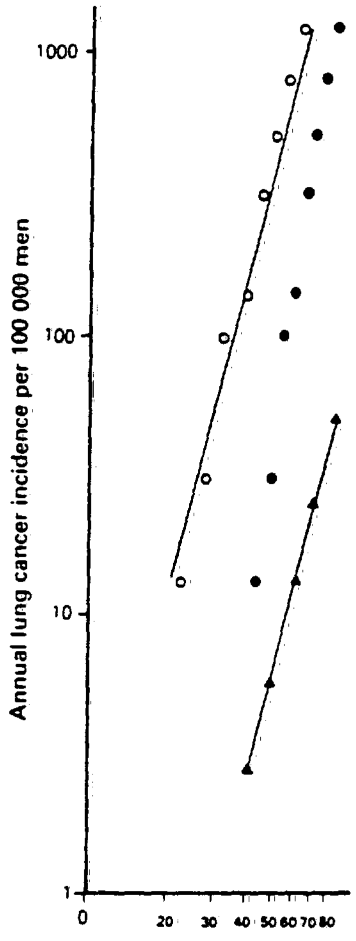

Figure 1 Incidence of bronchial carcinoma in non-smokers by age (▲) and in regular cigarette smokers by age (●) and duration of smoking (○). Solid lines have slope 4. Data for non-smokers from Doll (1971, Table VI). Data for smokers from Doll & Peto (1978) Table II, directly standardized for amount smoked.

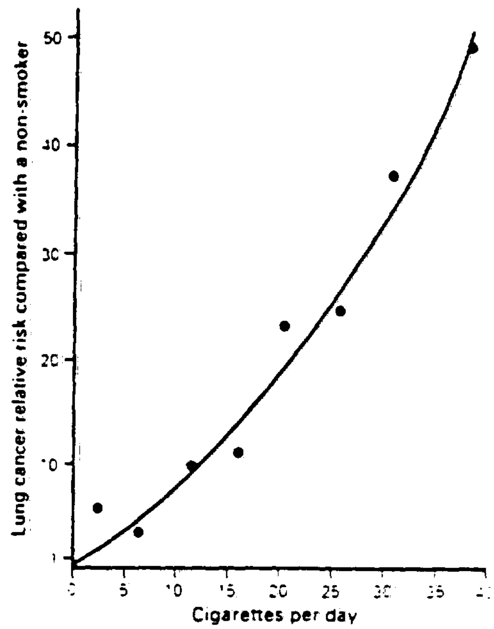

Figure 2 Comparison of dose-response observed in British doctors' study with that obtained from the proposed multi-stage model. ● – Relative risks indirectly standardized for age from Doll & Peto (1978), Table IV (Printed values have been divided by 0.081 so that 0 cigarettes per day takes value 1.) Solid line – Relative risks predicted from the model. Values plotted are weighted sums of age-specific relative risks with weights equal to those used by Doll & Peto (1978), Table IV, for indirect standardization.

with five stages in which cigarette smoke affects the first and the fourth stage provides a highly satisfactory description of the patterns of lung cancer observed among active cigarette smokers. The patterns of lung cancer risk predicted by the model when the quantity of cigarettes smoked per day is very low, such as might effectively be smoked under conditions of passive exposure, are then explored.

Active smokers

Data on the numbers of lung cancers diagnosed and the distribution of man-years from a 20-year prospective study of male British doctors have been published by Doll & Peto (1978) for people who either reported that they were lifelong non-smokers, or who reported that they had smoked cigarettes regularly since early adult life, without either giving up or changing their consumption by more than five cigarettes per day, and who also reported no current or previous use of cigars or pipe. The data are available in the form of numbers of diagnosed lung cancers and man-years at risk in Tables II and III of Doll & Peto (1978) by current age in five-year groups, and numbers of cigarettes smoked per day (Never smoked, 1–4, 5–9, 10–14, etc.).

The lung cancer risk at age t, as predicted by our multistage model, for an individual who started smoking at age s and from then on smoked c cigarettes per day, relative to a lifelong non-smoker, is given in the **Appendix**. It depends on two parameters, b_1 and b_4, which are respectively the proportional amounts by which the rate of transformations to the first and the fourth stages of the carcinogenic process are increased by each cigarette smoked per day; specifically a_1 becomes $a_1(1+cb_1)$ and a_4 becomes $a_4(1+cb_4)$ during the time in which c cigarettes per day are smoked. The values of the parameters b_1 and b_4 were estimated by the method of maximum likelihood, conditional on the total number of incident lung cancers in each age group, and using data from the British doctors' study for individuals who were aged from 40 to 79 years, and who smoked up to 40 cigarettes per day. We have ignored data on doctors who reported smoking more than 40 cigarettes per day, as did Doll and Peto in their analysis; a full discussion of the reasons for omitting them is given in Doll & Peto (1978). In the data all the doctors had started smoking when they were between 16 and 25 years old. In estimating b_1 and b_4 it was assumed for simplicity that all the smokers had started smoking at 20 years of age. This method of fitting enables the effect of cigarette smoking to be estimated in terms of relative risks. To make predictions in terms of absolute incidence rates we have assumed in what follows that the incidence rate in non-smokers at age 60 is equal to that observed in the data on non-smokers in Figure 1.

The estimated values for b_1 and b_4 are 0.29 and 0.37 with estimated standard errors of 0.32 and 0.35. The fit of the model to the British doctors' data is excellent. Pearson's goodness-of-fit statistic is 52.4 and the residual deviance is 51.1; both of these statistics have 54 degrees of freedom and thus provide no evidence of a poor fit to the data. A plot of standardized residuals against normal order statistics indicated that the model fitted the data well, and plots of residuals against both current age and number of cigarettes smoked per day gave no evidence of systematic departures from the model.

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The ability of the model to reproduce the main features of cigarette smoking, as observed in the British doctors' study, is illustrated in Figures 2 to 4. In Figure 2 it can be seen that the dose response relationship from the multistage model reproduces very closely the approximately quadratic relationship observed in the data. Figure 3 shows the annual incidence of lung cancer in smokers and non-smokers as predicted by the model. The predictions have been made assuming that all smokers started smoking on reaching age 20, and smoked 20 cigarettes per day. These values are similar to the average values of 19.2 years and 18 cigarettes per day observed in the British doctors' data. By comparing Figures 1 and 3 it can be seen that, once again, the proposed model reproduces very closely the patterns of increase in lung cancer incidence seen in the original data.

Figure 4a shows data on the risk of lung cancer among British doctors who stopped smoking, by time since stopping, relative to their risk at the time they stopped. For comparison, risks are shown on the same scale for continuing cigarette smokers and lifelong non-smokers. The beneficial effect of stopping smoking is evident within five years, and there is a possibility that the incidence rate may actually decrease during the first 10 years after stopping smoking. However, the data are too few to be certain that this is so, and it is clear that the risk keeps well above that for lifelong non-smokers (Doll, 1978). The equation predicting the effect of giving up smoking according to the multistage model is given in the **Appendix**, and it is illustrated in Figure 4b, where it is assumed that the smokers consumed 20 cigarettes per day from age 20 to age 50 and then stopped. As was seen in the doctors' study, the beneficial effect of stopping is seen after only a few years, and the risk among those who stopped is clearly intermediate between those seen in continuing smokers and in lifelong non-smokers. From the model predictions there is no suggestion that the relative risk falls below one in the first

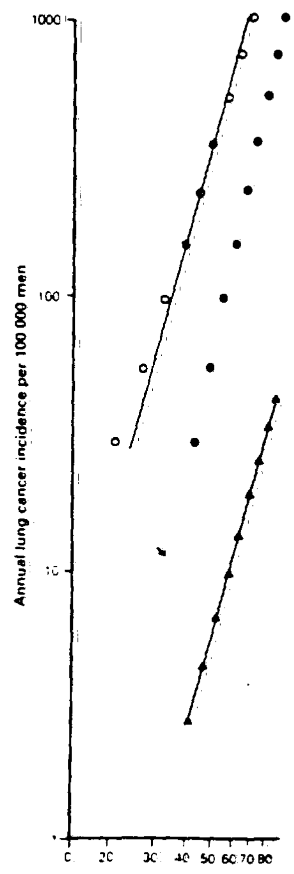

Figure 3 Incidence of bronchial carcinoma as predicted by the model in non-smokers by age (▲) and in smokers of 20 cigarettes per day from age 20 by age (●) and duration of smoking (○). Solid lines have slope 4.

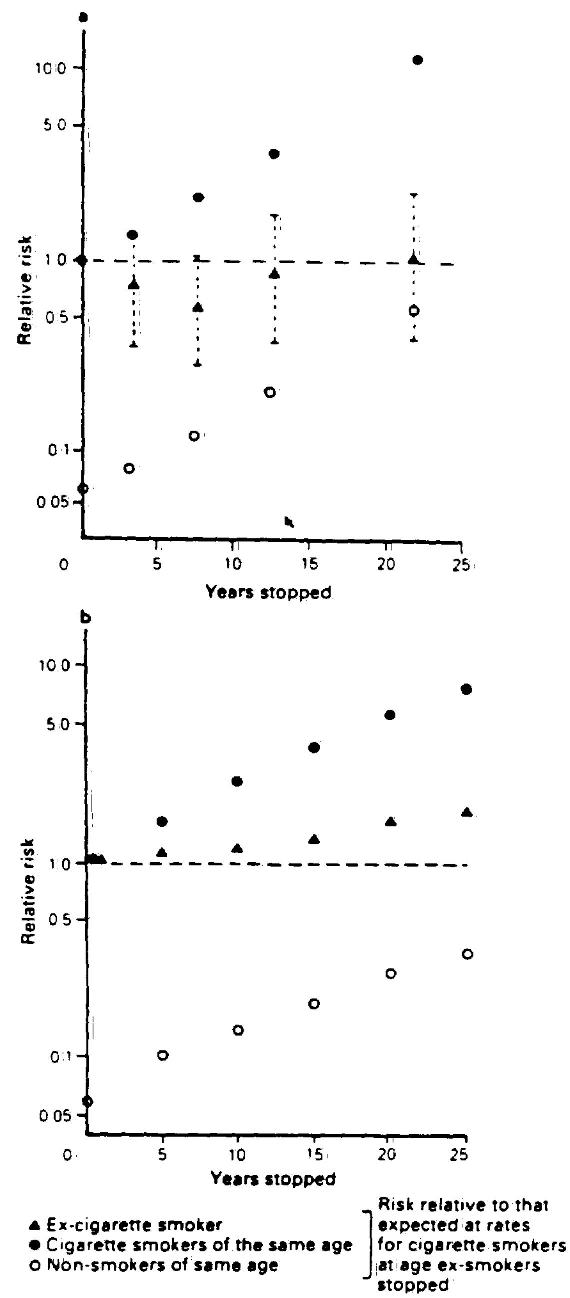

Figure 4 Comparison of the effect of stopping smoking observed in British doctors' study with that obtained from the proposed multistage model. Risk is measured relative to the risk in a regular cigarette smoker at the ages at which smoking was stopped (a) Data from British doctors' study, amd US non-smokers standardized for amount smoked at time of stopping (Data from Doll, 1978, chart 6, reproduced with permission.) (b) Predictions from the model, assuming smokers consumed 20 cigarettes per day from age 20 to age 50, and then stopped.

few years after stopping; and using the equation for the relative risk in an ex-smoker shown in the **Appendix** it can be shown that under the proposed model the incidence of lung cancer will never decrease below that already reached at the time of stopping smoking regardless of amount smoked or ages at starting and stopping. There is evidence from pathological studies of tracheo-bronchial trees that the number of atypical nuclei in the bronchial epithelium diminishes on cessation of smoking (Auerbach *et al.*, 1962), and this observation lends some support to the idea that the risk of lung cancer might actually decrease in the first few years after giving up smoking. However, the slight discrepancy between the observations on British doctors and the predictions from the model could also be accounted for by random variation, or by the fact that individuals who succeed in giving up smoking were less likely to inhale than continuing smokers (Doll & Hill, 1964).

Overall the ability of this multistage model to reproduce the main features of cigarette smoking, as observed in the British doctors' study seems remarkable.

Passive smoking

The predictions of the model when the number of cigarettes smoked per day is low, including the range of exposures indicated by the risks observed in epidemiological studies of passive smoking, are shown in Table I. The predictions have been made for an individual aged 65 assuming first that the individual was exposed continuously from birth, secondly that the individual was unexposed until age 20 but exposed continuously since then, as might happen for a non-smoking individual who married a smoker or started work in a smoky environment at age 20, and thirdly that the individual was exposed only between birth and age 20, as might occur in individuals whose parents smoked, but who were not otherwise exposed. A number of points emerge. First, on a relative scale at least, the risks are substantial. The predicted effect of smoking the equivalent of only one cigarette per day from birth to age 65 is to increase lung cancer risk by more than 75%, while if exposure starts at age 20 the risk is increased by 46% and if exposure is limited to childhood the risk is increased by 23%. Secondly, for exposures up to the equivalent of three cigarettes per day, exposure in childhood only is predicted to incur about half the increase in risk of exposure at the same level in adult life only. Thirdly, and most strikingly, although the risk is greater if exposure occurs both in childhood and in adult life than if it occurs in only one of the two periods, the drastic increase in risk with increasing duration of exposure, seen in active smokers, is absent. For example, exposure at the rate of one cigarette per day from birth to age 65 incurs only a 21% greater relative risk than exposure at the rate of one cigarette per day from age 20 to age 65 (1.77 compared with 1.46). Direct analogy with the effect of duration of smoking as seen in active smokers of around 20 cigarettes per day would have predicted nearly a four-fold increase.

The importance of duration of exposure in determining the increase in relative risk diminishes with diminishing level of exposure. This is illustrated in Table II where the lung cancer relative risks predicted by the model are shown for a wide range of levels of exposure. For smokers of 20 cigarettes per day, relative risks by age 60 are more than 50% greater than they were at age 40, but at low levels, such as half a cigarette per day, the proportionate increase in relative risk is less than 3% over the same period.

The above calculations have all been made assuming that the British doctors were not themselves exposed to passive smoke. As regards exposure in childhood this assumption is

Table I Effect of passive smoking on lung cancer risk at age 65, as predicted by the model

Effective passive smoking (cigarettes per day equivalent)	*Risk relative to a non-exposed non-smoker*		
	Exposure from age 0 to age 65	*Exposure from age 20 to age 65 only*	*Exposure from age 0 to age 20 only*
0.00	1.00	1.00	1.00
0.10	1.07	1.04	1.02
0.20	1.14	1.09	1.05
0.25	1.17	1.11	1.06
0.50	1.36	1.22	1.11
1.00	1.77	1.46	1.23
1.50	2.23	1.71	1.34
2.00	2.75	1.97	1.46
3.00	3.95	2.52	1.69
4.00	5.36	3.13	1.93
5.00	6.98	3.78	2.16

Table II Lung cancer risk predicted from the model for smoking a constant number of cigarettes per day starting at age 20. Figures shown are risks relative to that for a non-exposed non-smoker by current age and number of cigarettes per day

Current age	*Cigarettes per day*						
	0.1	*0.5*	*1.0*	*5.0*	*10.0*	*20.0*	*30.0*
40	1.036	1.184	1.37	2.99	5.31	10.96	17.94
50	1.040	1.202	1.41	3.33	6.36	14.50	25.42
60	1.042	1.216	1.44	3.64	7.33	17.90	32.71
70	1.044	1.228	1.47	3.91	8.21	21.01	39.39
80	1.046	1.238	1.49	4.14	8.99	23.76	45.32
Above relative risks divided by relative risk at age 40:							
40	1.000	1.000	1.00	1.00	1.00	1.00	1.00
50	1.003	1.016	1.03	1.12	1.20	1.32	1.42
60	1.006	1.027	1.05	1.22	1.38	1.63	1.82
70	1.008	1.037	1.07	1.31	1.55	1.92	2.19
80	1.009	1.046	1.09	1.39	1.69	2.17	2.52

probably reasonable, as all individuals would have dates of birth before about 1926. In the 1920s cigarette consumption among women (including the mothers of the British doctors) was very low, while that among men was less than in subsequent years (Lee, 1976). In contrast, passive exposure in adult life may well have been substantial in the doctors' cohort by present day standards, as the vast majority of men doctors included (Doll & Peto, 1976), smoked cigarettes in 1951 when the cohort was identified, and when there was little public awareness of the risks of either active or passive smoking. In order to illustrate the possible effect of passive smoking among the British doctors on the predictions shown in Table I, estimates of the parameters in the multistage model were recalculated assuming, as an example, that all the doctors, both smokers and non-smokers, were exposed to passive cigarette smoking at a rate equivalent to one cigarette per day throughout their adult life. The revised model predictions from this example are shown in Table III. The general effect of making the allowance for passive smoking is a small increase in the predicted relative risks which is of the order of 10 to 20% for passive smoking exposures of half to one cigarette per day equivalent. For exposures of five cigarettes per day, larger increases in relative risk are implied, and for an individual who has been exposed at a rate of five cigarettes per day from age 20 the predicted risk at age 65 relative to a lifelong non-smoker is increased by nearly 40% from 3.78 to 5.24. However the general conclusions based on the predictions in Table I remain unchanged. In practice non-smokers are, of course, likely to have much less passive smoking exposure than smokers; when this is taken into account the changes shown in Table III are, of course, reduced and the true effects are thus likely to be bounded by the results in Table I and Table III.

Discussion

Multistage models for the development of cancer are possibly no more than a crude mathematical description of a complex biological process. Nevertheless the proposed multistage model has been shown to provide an accurate coherent summary of the patterns of lung cancer risk among active smokers, ex-smokers, and non-smokers. It is likely therefore also to provide good estimates of the pattern of lung cancer risk following exposure equivalent to smoking between 0.1 and five cigarettes per day. It should also provide a reasonable guide to the consequences of environmental exposure to other people's smoke (passive smoking). It should in particular provide guidance on topics on which accurate human data is likely to remain sparse, such as the likely effects of variation in the age at which passive exposure began and of variation in the duration of such exposure, although of course in the absence of validatory data it cannot be concluded with certainty that the model predictions in this low dose range are correct.

Among active smokers, age at starting to smoke and duration of the smoking habit strongly determine the risk of lung cancer, and these features are accommodated in our model by the assumption that exposure to cigarette smoke affects the first stage. We therefore anticipated that the model would predict a substantial increase in relative risk for exposures starting in early childhood. However, our expectations were not supported by the model predictions, which indicate an increase in the relative risk of no more than about 20% for exposure starting at birth compared to exposure starting at age 20, for exposures equivalent to the range one tenth to one cigarette per day. If the 'adult exposure' had been assumed to start at an earlier age than 20, reflecting the fact that in recent surveys in Britain the median recalled age at starting to smoke is 16–17 (Wald *et al.*, 1988), the increase in relative risk for lifelong exposure, as compared with exposure in adult life only, would have been even smaller.

The relative risks associated with exposures in the range one tenth to one cigarette per day are less than two, and are thus smaller than the underlying background risk of lung cancer due to causes other than cigarettes. Exposure to at least some of these is likely to commence at birth or in early childhood. On this basis it is more helpful to think of the early commencement of passive smoking at rates equivalent to one cigarette per day or less as an increase in the dose of an existing carcinogenic exposure rather than an increase in the duration of passive smoking exposure.

In terms of the mathematical formulation of the model given in the **Appendix**, it is clear from the expression for $I(s,t)$, the incidence rate at age t in the smoker of c cigarettes per day since age s, that as c increases the term involving $c^2b_1b_4$, which involves duration to the fourth power, will begin to dominate. For small values of c (i.e. less than b_1^{-1} and b_4^{-1}) it can easily be shown that the term involving cb_4, which increases only very slowly with duration, will play the major role in determining the incidence rate for values of b_1, b_4, s and t that are of concern here. In non-mathematical terms this amounts to the fact that, for active smokers of a substantial number of cigarettes, the incidence rate of lung cancer is determined by the effect of smoking on both the first and the fourth stages. In contrast, at levels equal to the numbers of cigarettes effectively smoked by passive smokers, the effect of those cigarettes is primarily on the fourth stage, and its effect on the first stage is relatively minor.

Wald *et al.* (1986) have reviewed the 13 epidemiological studies of lung cancer and passive smoking which have been carried out in six different countries. When the results are combined, these studies suggest that the relative risk of lung

Table III Effect of passive smoking on lung cancer risk at age 65, as predicted by the model, allowing for passive smoking at a rate equivalent to smoking one cigarette per day from age 20 in the British doctors

	Risk relative to a non-exposed non-smoker		
Effective passive smoking (cigarettes per day equivalent)	*Exposure from age 0 to age 65*	*Exposure from age 20 to age 65 only*	*Exposure from age 0 to age 20 only*
0.00	1.00	1.00	1.00
0.10	1.09	1.06	1.03
0.20	1.19	1.13	1.05
0.25	1.23	1.16	1.06
0.50	1.49	1.33	1.13
1.00	2.07	1.68	1.25
1.50	2.75	2.05	1.38
2.00	3.51	2.44	1.51
3.00	5.31	3.29	1.76
4.00	7.48	4.22	2.03
5.00	10.01	5.24	2.29

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cancer among non-smokers living with smokers compared to non-smokers living with non-smokers is about 1.35. Wald *et al.* estimated that adjustment for the likely extent of misclassification of some current smokers and some ex-smokers as non-smokers (never-smokers) reduces this estimate to 1.30, but estimated that allowance for the fact that people living with non-smokers may still be exposed to other people's smoke increases the estimate to 1.53. (This latter adjustment is similar in magnitude to the effect of allowing for exposure to environmental tobacco smoke among the British doctors in estimating the parameters of our multistage model, see Table III.)

Although the US National Academy of Science's Committee on Passive Smoking (1986) accepted the estimates of Wald *et al.*, other authors have disputed them and claimed that the increased lung cancer risk seen among non-smokers exposed to passive smoking is largely the effect of bias due to the misclassification problems we mentioned above. For example, Lee (1987) suggested, on the basis of recent surveys carried out in the UK for the Tobacco Advisory Council, that the proportion of true ex-smokers amongst persons claiming to be lifelong non-smokers was double the estimate used by Wald *et al.* Lee also suggested that the average number of cigarettes per day smoked by current smokers claiming to be non-smokers was considerably more than estimated by Wald *et al.* and was at least half that of people admitting to being smokers. These assumptions lead to a much lower estimate for the lung cancer risk from passive smoking, and Lee concluded that almost no lung cancer is caused by passive smoking. In our opinion, Lee's estimate of the average number of cigarettes smoked per day (an important determinant in the risk estimation) among current smokers claiming to be non-smokers seems excessive, but it is hard to judge on the basis of published data how either the estimates of Wald *et al.* or Lee relate to the individual studies that led to the combined estimate of 1.35. Further work is required on the extent of misclassification in the actual populations in which the epidemiological studies were done.

The biological marker that has proved most useful in assessing average daily exposure to tobacco smoke among those exposed to passive smoking is cotinine (Committee on Passive Smoking, 1986). Recent studies in the UK measuring cotinine levels in active and passive smokers in plasma, urine and saliva indicate that levels in passive smokers are in the range 0.6 to 0.8% of those in active smokers (Jarvis *et al.*, 1984). However the half-life of cotinine in non-smokers may be roughly 50% longer than in active smokers (Sepkovic *et al.*, 1986). Active smokers in the UK currently smoke between 15 and 20 cigarettes per day (Wald *et al.*, 1988) and so the cotinine measurements indicate an exposure of between 0.06 and 0.11 cigarettes per day. According to the proposed multistage model, a relative risk of 1.5, as estimated by Wald *et al.* (1986) from the epidemiological studies of exposure to passive smoking, results from the effective exposure to about half to one cigarette per day. Thus the cotinine measurements indicate a level of exposure that is between one seventeenth and one fifth the amount indicated by our model. This estimate is based on cigarettes available during the 1950s and 1960s and used by the men in the British doctors' study: to the extent that currently available cigarettes are associated with lower lung cancer risks these factors would be somewhat reduced. A further difficulty is that the relationship between the amount of nicotine absorbed and the amount of tar deposited on the bronchi is not necessarily the same in passive as in active smoking, and this could influence the postulated risk in either direction. We conclude, however, that the relative risks of lung cancer due to passive smoking as estimated by Wald *et al.* (1986) seem to be at variance with the numbers of cigarettes per day equivalent estimated from cotinine measurements. This discrepancy remains even when allowance is made, within the framework of our model, for the fact that passive smoking may commence in early childhood, and when the parameters of the model are estimated allowing the British doctors' themselves to have been exposed to passive smoking.

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Appendix

It is assumed that there are five ordered stages in the carcinogenic process, that the rate of transition of a cell from stage to stage is constant in time apart from specified increases in the exposure intensity, that tumour growth time is negligible and that tumours are rare.

Let $P_4(t)$ be the probability that a specific cell has undergone four changes at time t. When exposure is to background exposure intensities only, let $P_4(t)$ be denoted by $P_4^0(t)$, and let the transition rates from stage to stage be a_i, $i = 1, \ldots 5$. It follows that

$$P_4^0(t) = k_1 \int_0^t a_4 \int_0^{x_4} a_3 \int_0^{x_3} a_2 \int_0^{x_2} a_1 \, dx_1 dx_2 dx_3 dx_4$$

$$= k_1 a_4 a_3 a_2 a_1 t^4 / 4!$$

where k_1 is a constant. If $I^0(t)$ is the associated incidence rate of lung cancer for a background only exposed individual at age t, then

$$I^0(t) = k_2 a_5 P_4^0(t)$$

$$= k_3 a_5 a_4 a_3 a_2 a_1 t^4 / 4!,$$

where k_2 and k_3 are constants that include an allowance for the number of cells in the individual at risk of developing lung cancer.

For an individual who begins to smoke cigarettes at age s at the rate of c cigarettes per day and continues to smoke until age t, let the transition rate from stage zero to stage one be altered from a_1 to $a_1(1 + cb_1)$ after age s, and similarly let that for stage three to stage four be altered from a_4 to $a_4(1 + cb_4)$. In such a smoker, let the probability that in any individual cell the first $(i-1)$ transitions occur before age s, and the remaining $(5-i)$ after that age be denoted by $P_4^{(i)}(s, t)$ for $i = 1, \ldots 4$. Then

$$P_4^{(i)}(s, t) = k_1 \int_s^t a_4^* \int_s^{x_4} a_3^* \ldots \int_s^{x_{i+1}} a_i^* dx_i \ldots dx_4$$

$$\times \int_0^s a_{i-1} \int_0^{x_{i-1}} a_{i-2} \ldots \int_0^{x_2} a_1 \, dx_1 \ldots dx_{i-1}$$

where $a_4^* = a_4(1 + cb_4)$, $a_3^* = a_3$, $a_2^* = a_2$, and $a_1^* = a_1(1 + cb_1)$, and the probability, $P_4^c(s, t)$, that the smoker has a specific cell that has undergone 4 changes at time t is given by

$$P_4^c(s, t) = \sum_{i=1}^{5} P_4^{(i)}(t).$$

It follows straightforwardly from substitution that the lung cancer incidence rate at age t in the smoker of c cigarettes per day since age s, $I^c(s, t)$, is given by

$$I^c(s, t) = k_3 a_5 a_4 a_3 a_2 a_1 t^4 / 4! \times [1 + cb_1(t - s)^4 / t^4$$

$$+ cb_4(1 - s^4/t^4) + c^2 b_1 b_4 (t - s)^4 / t^4]$$

and the age-specific relative risk for such an individual compared to a lifelong non-smoker of the same age, $R^c(s, t)$, is given by

$$R^c(s, t) = 1 + cb_1(t - s)^4/t^4 + cb_4(1 - s^4/t^4) + c^2 b_1 b_4 (t - s)^4 / t^4.$$

By using a similar argument it can be shown that for an individual of age t who began to smoke cigarettes at the rate of c per day until stopping at age u, the age specific risk compared to a lifelong non-smoker, $R^c(s, u, t)$ is given by

$$R^c(s, u, t) = 1 + cb_1\{(t - s)^4 - (t - u)^4\}/t^4 + cb_4(u^4 - s^4)/t^4$$

$$+ c^2 b_1 b_4 (u - s)^4 / t^4.$$

LETTERS TO THE EDITOR

Lung cancer and passive smoking

Sir – Darby and Pike (1988; **58**, 825) use a multistage model together with data on smoking and lung cancer to estimate the effect of exposure to other people's smoke on the risk of lung cancer. They give examples of the expected risks according to levels of passive smoking, expressed in terms of the number of equivalent cigarettes per day actively smoked.

In our review of the epidemiological studies of lung cancer and exposure to other people's tobacco smoke, we estimated that the risk of lung cancer among non-smokers living with smokers was about 50% higher than the risk in non-exposed non-smokers (Wald *et al.*, 1986). This risk, according to Darby and Pike, is approximately equivalent to smoking 0.5 cigarettes a day from birth to age 65 years, and they conclude it is some 5–17 times too high in the light of the level of biochemical markers of tobacco smoke exposure that have been measured in non-smokers. We did not think that this was so in our review and we are still of the opinion that the biochemical data are broadly in line with the estimates of risk based on epidemiological studies.

In our study of the principal marker, urinary cotinine (Wald *et al.*, 1984; Wald & Ritchie, 1984), the mean level in non-smokers who lived with smokers was about 1.5% (cited in Wald *et al.*, 1986; US National Academy of Science's Committee on Passive Smoking, 1986; Barlow & Wald, 1988) of the mean level found in active smokers, equivalent to smoking about 0.3 of a cigarette per day if active cigarette smokers typically smoke 20 cigarettes a day (1.5% of 20). An exposure equivalent to smoking 0.3 of a cigarette a day is similar to the estimate of 0.5 of a cigarette that would, according to the model adopted by Darby and Pike, 'explain' a 50% higher risk of having lung cancer in passive smokers.

The half-life of serum cotinine in non-smokers may be about 50% greater than in smokers and, if this were the case, our estimate would become 0.2 instead of 0.3.

The principal reason for the difference in the estimates of Darby and Pike and our own arises from their use of data on urinary cotinine levels in passive smokers showing levels of 0.6–0.8% of active smokers (Jarvis *et al.*, 1984). We believe that the figure of 1.5% is more appropriate than that of Jarvis and his colleagues because they did not classify cotinine levels by the smoking habit of the person the subject lived with, which is needed when comparing the results with similar epidemiological data. They also excluded self-reported non-smokers with plasma cotinine levels greater than 20 ng ml^{-1}, which is likely to have excluded some individuals who, while not smokers themselves, were nonetheless heavily exposed to environmental tobacco smoke.

Bearing in mind the recognised uncertainties and difficulties involved in extrapolating from the biochemical data to the epidemiological data, there does not seem to be an obvious discrepancy between the two.

Yours etc.

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Response to the letter from Dr. Wald

Sir – Wald and his colleagues question the conclusion we reached in our recent paper that there is a discrepancy between the low levels of exposure indicated by cotinine measurements in those passively exposed to cigarette smoke and the high relative risk for lung cancer of 1.5 from passive smoke exposure estimated by Wald *et al.* (1986) from epidemiological studies.

As noted by Wald and his colleagues, an important reason for the difference in our estimates is that we considered the urinary cotinine levels of passive smokers to be 0.6–0.8% that of active smokers, whereas they considered a figure of 1.5% to be more appropriate. Our figures were derived from Tables I and II of Jarvis *et al.* (1984). These data compared 27 non-smokers reporting 'some' or 'a lot' (there was no difference in the data from these two groups) of exposure to passive smoke to 94 smokers. The mean urinary cotinine for these 27 non-smokers reporting passive smoking exposure was 8.8 ng ml^{-1} while that for the smokers was 1,391.0, so that the ratio is 0.63% (8.8/1,391.0). A slightly higher figure is obtained if plasma and salivary values are considered, and for this reason we gave a range of 0.6–0.8%. In addition to these 27 non-smokers, there were 79 non-smokers with 'none' or 'a little' exposure to passive smoke, and 21 persons claiming to be non-smokers but whose level of plasma cotinine was according to the authors incompatible with their claim. Only one of the 100 accepted non-smokers (mean plasma cotinine, 1.5 ng ml^{-1}) had a plasma cotinine value above 10 ng ml^{-1} (actual value 14 ng ml^{-1}), whereas all the 21 'deceivers' had values above 20 ng ml^{-1} with a mean value of 239.3, which was 87% of the mean value for the declared smokers. Excluding those deceivers seems completely justified to us.

Taking, as do Wald and his colleagues, our high figure of 20 cigarettes per day consumption for smokers, and allowing a factor of 2/3 to account for the different half-life of cotinine in smokers and non-smokers, the cigarette equivalent exposure of passive smokers is estimated to be 2/3 × 0.63% of 20 cigarettes per day or 0.08, which is still only one-sixth

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of the lowest equivalent amount (0.5 cigarettes per day) that the multistage model predicts could cause a relative risk of 1.5. Clearly classification of cotinine levels by the smoking habit of the person with whom the subject lived might alter these figures, but we have been unable to find any data subdivided in this way in which efforts have also been made to exclude deceivers.

As we stated in our paper, it may simply be that cotinine is not an adequate measure of the exposure of non-smokers to the carcinogenic components of cigarette smoke. It is also possible that, given all the uncertainties and unknowns involved, in particular knowledge of the comparability of the passive smoke exposure of those in the lung cancer case-control studies to those in the surveys of Jarvis *et al.* (1984) and of Wald and Ritchie (1984), a factor of six is effectively good agreement. Careful studies may be able to resolve this issue.

Yours etc.

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WEAKNESSES IN RECENT RISK ASSESSMENTS OF ENVIRONMENTAL TOBACCO SMOKE

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ABSTRACT

Epidemiological evidence of increased lung cancer risk in never smokers married to smokers has been used to estimate annual deaths from environmental tobacco smoke (ETS) exposure. Such estimates are very much higher than those based on dosimetric considerations and misleadingly ignore major weaknesses in the epidemiology. Some authors overestimate total lung cancers occurring in never smokers. There is no scientific basis for extending risk assessments to include deaths from other causes, from workplace exposure to ETS, and among ex-smokers. Recent risk assessments by Wells, by Repace and Lowrey, and by Kawachi and colleagues are given particular attention.

INTRODUCTION

In 1986 four authorities reviewed the evidence on the relationship of environmental tobacco smoke (ETS) and health (1-4). There was agreement that there was inadequate evidence to determine whether ETS caused heart disease or cancers other than the lung. With regard to lung cancer views were more conflicting. The International Agency for Research on Cancer (1), while noting that "several epidemiological studies have reported an increased risk of lung cancer in non-smoking spouses of smokers" pointed to "substantial difficulties" and errors that "could arguably have artefactually depressed or raised estimated risks" so that each study "is compatible either with an increase or with an absence of risk". The Australian National Health and Medical Research Council (2) noted that "the evidence that passive smoking causes lung cancer is strongly suggestive" and, although pointing to difficulties in many studies that "preclude a conclusive interpretation", stated that "passive smoking gives rise to some risk of cancer". The US Surgeon General (3) concluded that "involuntary smoking is a cause of lung cancer" but that quantification of the risk for the US population "is dependent on a number of factors for which only a limited amount of data are currently available". The US National Research Council (4) noted that a "summary estimate from epidemiological studies places the increased risk of lung cancer in non-smokers married to smokers compared with non-smokers married to non-smokers at about 34%" and considered that, though "to some extent, misclassification bias may have contributed to the results reported in the epidemiological literature", the "bias is not likely to account for all of the increased risk".

Although one of the four authorities felt it premature to conclude cause and effect, and two who thought cause and effect could be concluded, felt it could not be quantified, there has been an increasing tendency to carry out risk assessments to estimate annual numbers of deaths due to ETS. The purpose of this paper is to underline a number of problems in conducting such risk assessments, and to comment critically on three that have recently been published. The first, by Wells (5), estimated that annually in the United States 46,000 deaths per year occurred among non-smokers (i.e. never plus ex-smokers combined) due to ETS exposure at home and at work. 3,000 were from lung cancer, 11,000 from other cancer and 32,000 from heart disease. The second, by Kawachi and colleagues (6), estimated that annually in New Zealand 273 deaths per year occurred among never smokers, 30 from lung cancer and 243 from ischaemic heart disease; 95 deaths were from at home exposure and 178 from at work exposure. The third risk assessment, by Repace and Lowrey (7), was based on a review of nine

other risk assessments for lung cancer. They noted that "excluding one study whose estimate differs from the mean of the others by two orders of magnitude, the remaining risk assessments are in remarkable agreement. The mean estimate is approximately 5000 ± 2400 non-smokers' lung cancer deaths per year in the US".

This paper starts by discussing risk assessment for lung cancer among never smokers based on epidemiological data in relation to spouse smoking, this being the area most intensively studied. Following this problems resulting from extending the risk assessment to cover other diseases are discussed, as are those caused by considering workplace as well as at home ETS exposure. Finally, some other issues are considered.

LUNG CANCER IN NEVER SMOKERS IN RELATION TO ETS EXPOSURE FROM THE SPOUSE

An up-to-date review of the evidence (8) shows there are 27 epidemiological studies of lung cancer (involving nine or more cases) in which risk in never smokers could be related to the smoking status of the spouse (or in five studies to an alternative index of at-home exposure). Eleven studies were conducted in the US, eleven in Asia and five in Europe, involving a total of 2350 lung cancer cases with relevant data, 90% of these being females. 26 of the 27 studies provide estimates of relative risk in relation to this index of ETS exposure for females; values range from just under 1.0 to just over 2.0. Five are statistically significantly positive and 20 estimates are greater than 1.0. Taken as a whole the data show a positive relationship - the median is about 1.25. Based on 17 of these studies, using formal meta-analytic techniques which weighted studies on sample size but not on quality of evidence, Wells (5) gave an average relative risk of 1.44, with 95% confidence limits 1.26 to 1.66. The data for males are more variable, being based on 11 studies often with small numbers of deaths. Seven relative risks were greater than 1, one significantly so, with one equal to 1 and three less than 1. The median is similar to that for females.

The epidemiological evidence has been used for the risk assessments of Wells (5) and Kawachi *et al* (6). It has also been used for a number of the risk assessments cited by Repace and Lowrey (7). This is only valid if the epidemiological evidence itself is sound and not subject to material bias. In order to investigate this issue, two questions will be addressed; first, "Is the magnitude of the risk plausible based on what is known about the extent of exposure?" and second, "Are there weaknesses and sources of bias in the epidemiology which could invalidate the approach?"

Dosimetric considerations.

If lung cancer risk, relative to a non ETS exposed never smoker, is RE in an ETS exposed never smoker and RS in an ever smoker, then the ratio of excess risks $X=(RE-1)/(RS-1)$ is an indicator of the relative effects of ETS exposure alone and of smoking. Since risk associated with smoking is approximately proportional to number of cigarettes smoked, one might expect, were the epidemiology unbiassed, that X would be similar to the ratio of relevant smoke constituents from ETS exposure and from smoking. Table 1 shows, in rank order, estimates of X based on data for 18 studies in females and 7 studies in males. In females, almost half (8/18) of estimates are 0.2 or greater with the median value 0.14. For males, the results vary more and are based on many less data points, but the conclusions to be drawn are similar - namely that the epidemiological evidence, if unbiassed, suggests that the extent of exposure from ETS (from spousal smoking) is something like 10-20% of that from active smoking.

It is clear the ratio of exposure from ETS and exposure from active smoking is much lower than 10-20% for those smoke constituents that are commonly used as markers. In a large nationally representative study in the UK (27), mean salivary cotinine levels in non-smokers married to non-smokers, in non-smokers married to smokers and in smokers were respectively 1.22, 3.78 and 331 ng/ml in males and 0.76, 2.21 and 328 ng/ml in females, giving a relative exposure for ETS to active smoking of 0.8% in males and 0.4% in females. Repace and Lowrey (7) give a slightly higher figure, noting that non-smokers have of "the order of 1% of nicotine uptake of smokers" but it is still an order of magnitude less than the 10-20% one requires to align with the epidemiology. Differences in clearance rates of cotinine reported between non-smokers and smokers are too small to affect this gross discrepancy materially; in any case, since the half-life seems to be longer in non-smokers it would increase the discrepancy (28), not reduce it as Repace and Lowrey (7) claim.

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TABLE 1 Comparability of relative risks due to ETS exposure (from spouse) and active smoking

Study	(ref)	Sex	RE*	RS**	X+
Inoue	(9)	Female	2.55	4.25	0.48
Geng	(10)		2.16	4.18	0.36
Trichopoulos	(11)		2.08	4.37	0.32
Akiba	(12)		1.52	3.24	0.23
Brownson	(13)		1.82	4.75	0.22
Koo	(14)		1.55	3.56	0.21
Lam 1	(15)		2.01	5.94	0.20
Hole	(16)		1.89	5.43	0.20
Lam 2	(17)		1.65	4.97	0.16
Hirayama	(18)		1.38	4.12	0.12
Gao	(19)		1.19	3.15	0.09
Wu	(20)		1.20	3.31	0.09
Correa	(21)		2.07	14.10	0.08
Humble	(22)		2.34	28.53	0.05
Svensson	(23)		1.26	7.17	0.04
Lee	(24)		1.03	4.70	0.01
Buffler	(25)		0.80	5.91	-0.04
Chan	(26)		0.75	3.07	-0.12
Akiba	(12)	Male	2.10	3.21	0.50
Hirayama	(18)		2.34	4.39	0.40
Hole	(16)		3.52	15.88	0.17
Humble	(22)		4.19	29.36	0.11
Correa	(21)		1.97	30.15	0.03
Lee	(24)		1.31	12.02	0.03
Buffler	(25)		0.51	7.03	-0.08

* Risk of ETS exposed never smoker relative to non ETS exposed never smoker

** Risk of ever smoker relative to non ETS exposed never smoker

\+ Ratio of excess risks, e.g.for first study 0.48 = (2.55-1)/(4.25-1)

N.B. Risks given are unstandardised for age since standardised estimates were not available in many studies and generally differed little from unstandardised estimates where both were available.

Estimates of relative exposure based on inhaled smoking-related particulates show an even greater discrepancy. Arundel *et al* (29) have estimated that for the US average daily inhaled particulate ETS exposure for all never smokers is 0.62 mg/day for men and 0.28 mg/day for women as against 387 mg for men and 311 mg for women who currently smoke. Since ETS exposure of exposed non-smokers is about 3 times that of all non-smokers (27), one can calculate that the ratio of average exposure for ETS to active smoking is about 0.4% in men and 0.2% in women, similar to an estimate of 0.3% given by Repace and Lowrey (7) based on their own work.

Arundel *et al* (29) pointed out retention of smoking related particulates is much higher in smokers (80%) than in non-smokers(11%). They estimated a relative exposure for ETS to active smoking of around 0.03-0.04% (29). Using radiotracer techniques, a similar, very low ratio of 0.02% has been estimated based on particulate deposition in the trachea-bronchial region (30).

While both ETS and mainstream smoke contain a wide variety of chemicals, and relative exposure of passive and active smokers will vary quite widely according to which chemical is used as the marker - the factor being higher for vapour phase than for particulate phase compounds (31) - there is certainly strong evidence of a marked discrepancy between the epidemiology and dosimetry. Indeed, since it is commonly believed lung cancer in smokers is associated with deposition of particulate matter in the lung - the basis of "tar" reduction programmes - the discrepancy seems very large, by two or even three orders of magnitude.

One implication is that risk assessments based on dosimetric evidence are likely to give substantially lower estimates than those based on the epidemiological evidence. Another implication is that it gives reason to doubt the epidemiology, and to look for sources of bias.

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Risk assessments based on dosimetry versus those based on epidemiology.

Let us consider the situation with regard to the three risk assessment papers which are being studied in detail. All three have different approaches.

Kawachi *et al* takes the epidemiology at face value and do not attempt risk assessment based on dosimetric evidence (except vide infra to adjust relative risks for at home exposure to those for at work exposure). The discrepancy between the dosimetry and the epidemiology is not even mentioned.

Wells (5) also bases his risk assessment on the epidemiology. However he does note that the mortality observed for passive smoking is "rather high" relative to the deposited dose of particulate, contrasting relative factors for passive to active smokers of 0.25% for "smoke retention" (Arundel's figures cited above suggest 0.03-0.04%) and 2.9% for lung cancer (Table 1 suggests 10-20%). He believes the differences are due to differences in chemistry and physics between active and passive smoking, and essentially does not doubt the validity of the epidemiology.

Repace and Lowrey (7) review risk assessments based both on dosimetric and epidemiological evidence. While this should have revealed major differences between estimates based on the two methods of risk assessment they in fact claim "remarkable agreement". There are many reasons for this erroneous conclusion:

i) They rejected the estimate of Arundel *et al* (29), based on retained particulate matter, because it differs from the mean of the others by two orders of magnitude.
ii) They misquote Robins' work in the NRC report (4). They cite his estimates of 2500-5200 US deaths in lifelong non-smokers per year from passive smoking as being dosimetrically based when in fact they clearly are epidemiologically based. Robins also provides much lower estimates of 45-396 deaths based on respirable suspended particulates, but Repace and Lowrey totally ignore these.
iii) They quote an early paper by Fong (32), which assumed that the extent of exposure from ETS was of order 2% to 8% that from active smoking, a relative factor far higher than indicated by the more recent data summarized in the previous section.
iv) They omit their own dosimetrically based estimate because it is "inconsistent with the epidemiology of passive smoking". It is hardly surprising they get "remarkable agreement" if they reject estimates that do not agree!

Table 2 presents the various estimates for the studies reviewed by Repace and Lowrey (7). The epidemiologically based estimates are reasonably consistent and high. The dosimetrically based estimates are much lower. How much lower depends on the smoke constituent used for extrapolation.

Weaknesses of the epidemiology.

Epidemiology is imprecise. Various sources of bias can produce spurious relative risks of 2 or even more (38). Since the relative risks seen for ETS exposure are well within this range, and since they seem inconsistent with the dosimetric evidence, it is important to examine the epidemiological evidence critically. Six potential sources of bias are considered below.

Misclassification of diagnosis.

Of the 27 epidemiological studies of ETS and lung cancer, three were prospective and based diagnosis on death certificates, and only 15 used only (or virtually only) histologically confirmed cases. Faccini (39) has discussed the dangers of misdiagnosis, particularly of primary breast cancer as lung adenocarcinoma. The magnitude and extent of bias from this source is, however, unclear. Random misdiagnosis would tend to reduce the relative risk, but differential misdiagnosis might increase it. In theory differential misdiagnosis might occur if a risk factor for the misdiagnosed disease is correlated with ETS exposure, or if knowledge of ETS exposure by the doctor affects diagnostic procedures, but there is no direct evidence of this.

Misclassification of ETS exposure.

None of the studies had any objective measure of ETS exposure, either from ambient air measurements in the home or workplace or from measurements of levels of smoke constituents in body fluids. All information came from questionnaires. While random misclassification of exposure will tend to dilute associations, it is possible that in case-control studies some recall bias might have occurred, with cases overestimating exposure relatively to

controls in an attempt to rationalize their disease. This would probably have been less important for relatively "hard" questions such as those relating to whether the spouse smoked than for more "soft" questions on extent of exposure.

Publication bias.

There is strong reason to believe (40) that scientists are less likely to submit, and journals less likely to accept, papers showing no association than those showing a positive association. If so, published evidence tends to overestimate the true association of a factor with a disease. Since ETS has been the subject of much attention in recent years and since a relatively large number of unpublished null studies would be needed to counterbalance the high proportion of studies of spouse smoking and lung cancer showing a positive association, it would seem unlikely non-reporting bias could fully explain the overall positive relative risk. However the fact that the studies showing the highest relative risk are based on significantly smaller numbers of cases than the studies showing the lowest relative risks (8) is consistent with the notion that small null studies do not get published, and suggests some publication bias exists.

TABLE 2 Estimated number of lung cancer deaths occurring in US never smokers from ETS exposure in 1988 (adapted from Repace and Lowrey (7))

Study	(ref)	Method of estimation	Estimate *
Wald	(33)	Epidemiological	5210
Repace & Lowrey	(34)	Phenomenological **	4310
Robins	(4)	Epidemiological	4150
Wigle	(35)	Epidemiological	3650
Kuller	(36)	Epidemiological	3500
Wells	(5)	Epidemiological	2130
Fong	(32)	Dosimetric - 2% to 8% of effect	1860
Russell	(37)	Dosimetric - nicotine	710
Repace & Lowrey	(34)	Dosimetric-respirablesuspended particulates	490
Robins	(4)	Dosimetric +	240
Arundel	(29)	Dosimetric - retained particulate matter	40

* As given in (7), rounded, or converted from estimate for nonsmokers. Dosimetric estimate for Robins study added.

** Based on comparison of lung cancer rates in never smoking SDAs (Seventh Day Adventists) and non SDAs (uncorrected for numerous lifestyle factors on which SDAs and non SDAs are known to differ).

\+ Assuming a non-exposed non-smoker inhales the equivalent of 0.01 cigarettes per day. Robins gives 0.0001-0.005 cigarettes per day for the equivalent in terms of respirable suspended particulates.

Poor design of some studies.

Of the 27 studies which provided information on ETS and lung cancer, 24 were of case-control design. There were clear weaknesses in design in a number of the case-control studies. One study (10) did not even state what the control group was. Four studies (9, 12, 21, 25) included some patients or decedents with smoking associated diseases in their control group. More seriously there were systematic differences in study procedure between cases and controls in a number of studies. In three studies where the case might have been alive or dead (13, 22, 41) the controls were not matched on vital status. Two studies (11, 15) used cases and controls from different hospitals. Two studies (17, 23) interviewed cases in hospital and some or all controls elsewhere. In three studies (13, 21, 22) the proportion of next-of-kin respondents was substantially higher for cases than controls. Although difficult to quantify the effect of such procedural differences it is notable that for females the observed relative risk in the eight studies showing differences was higher (median 1.9) than in the 17 studies where like was being compared with like (median 1.2, p on rank test <0.05). It is also worth noting that three studies (12, 25, 42) obtained a high proportion of responses from next-of-kin and that in one of these (42), no association between lung cancer risk and spouse smoking was seen when the

subject herself reported the information, but a 3-fold relative risk was seen when the information was obtained from a daughter or a son.

Confounding.

There were 22 studies in which the index of ETS exposure used was smoking by the husband. One would have thought that the standard procedure would have been to present an age-adjusted comparison of married never smoking women whose husbands were non-smokers with married never smoking women whose husbands were smokers, and to also present a relative risk adjusted further for other potentially confounding factors known to affect risk of lung cancer. It was clear this standard procedure was not kept to. About half of these studies included unmarried women in their non-exposed group so that there was a confounding between marital status and ETS exposure. Three of the 22 studies (11, 15, 43) and also one of the other five (26) did not adjust for age at all while in three others (10, 17, 21), although cases and controls were age-matched initially, the error was made of failing to age adjust after the never smokers were selected out. Almost half the studies failed to take into account any other confounding factors and of the remainder most looked at only quite a limited number of possible such factors. Those few studies which looked at a reasonable number of confounders were generally those where no significant effect of ETS exposure had been seen anyway. Koo (44) compared never smoking women whose husbands did or did not smoke on a wide range of factors and found that those whose husbands did not smoke were "better off in terms of socio-economic status, more conscientious housewives, ate better diets, and had better indices of family cohesiveness".

Misclassification.

It is amply documented that active smoking is positively associated with lung cancer and also that smokers tend preferentially to marry smokers more often than would be expected by chance. As a result, even if ETS had no effect whatsoever on lung cancer risk, a spurious positive association between spouse smoking and lung cancer risk will be seen if a proportion of ever smokers are misclassified as never smokers (27). The relationship between the magnitude of this bias and the misclassification rate can be calculated theoretically given the degree of between spouse smoking concordance, the observed proportion of ever smokers, the observed proportion of never smokers who are married to smokers, and the observed relative risk in relation to active smoking. Table 3 shows this relationship for four scenarios: US women, US men, Asian women and Asian men. The misclassification bias is much larger where the proportion of smokers is larger, and where the relative risk in relation to active smoking is larger. In order to achieve a bias of 1.4 for example, one would need less than a 1% misclassification for US men, about a 2% misclassification for Asian men, about a 5% misclassification for US women and about a 30% misclassification for Asian women. Elsewhere (44) I have reviewed in detail the published evidence on the levels of misclassification actually determined in over 100 studies. In studies of self-reported non-smokers under no special pressure to deny smoking, biochemical tests suggested that on average around 4% were actually current smokers, with 1 to 2% current regular smokers. In addition to the misclassified current smokers, studies in which subjects were asked questions on multiple occasions have shown a somewhat larger number of ex-smokers misclassified as never smokers. The evidence is certainly consistent with misclassification bias being of major importance in the US (and European) studies. However there is virtually no good evidence on misclassification rates in Asian populations. There has long been speculation that rates may be particularly high among women in Japan, where smoking is not considered socially acceptable. A survey of Tokyo University freshwomen (46), among whom 55% of smokers reported that their family did not know they smoked, tends to confirm this. However until cotinine studies are conducted to find out the true situation the extent of bias caused by misclassification in Asian studies will remain unclear.

Misclassification also leads to overestimation of the total number of lung cancers among never smokers. This is considered below under "other issues".

Conclusion.

The answers to the two questions posed earlier are clear. The epidemiology has indicated a magnitude of risk in relation to spouse smoking that is implausibly large compared with what is known about the extent of ETS exposure involved. There are clear weaknesses and sources of bias in the epidemiology which could invalidate risk assessments based on it. The most important of these are misclassification bias and failure properly to compare like with

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like in case-control studies, but failure to properly take confounding variables into account and publication bias are also relevant.

All three risk assessments criticised in this document take the epidemiology virtually at face value, with no real discussion at all of its weaknesses. Thus Kawachi *et al* (6) mentions only publication bias (and dismisses it), while Wells (5) considers only misclassification bias (and then inadequately corrects for it). Repace and Lowrey (7) do not discuss any sources of bia at all (though some of the authors whose studie they review do so). No reasonable scientifi criteria are used to decide what constitutes a vali study before it can be included in a ris assessment - studies conducted with complet disregard of basic scientific principles ar included as if they were as valid as carefull designed studies.

TABLE 3 Bias due to misclassification in four scenarios.

Scenario	% Ever Smoked	% ETS Exposed	RR for Smoking	Misclassification Rate	Bias
US women	49.0	54.3	6.73	1%	1.06
				2%	1.12
				5%	1.35
				10%	2.02
US men	77.1	38.7	11.83	1%	1.52
				2%	2.38
Asian women	24.5	56.9	2.99	10%	1.07
				25%	1.26
				40%	1.73
				50%	2.82
Asian men	80.8	6.6	3.48	1%	1.20
				2%	1.42
				5%	2.36

N.B. No effect of ETS and between spouse concordance ratio of 3.0 assumed. % ever smoked, % ETS exposed and RR (relative risk) for active smoking estimated from those studies providing relevant data. See (8) for further details.

EXTENDING RISK ASSESSMENT TO COVER DISEASES OTHER THAN LUNG CANCER

Heart disease.

In the risk assessment by Wells (5), heart disease deaths formed 70% of the total. In that by Kawachi *et al* (6), they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion.

Wells (5) cites data from six published studies (18, 24, 47-50) and one unpublished study (51). Of these seven studies, five (16, 24, 48, 50, 51) were based on very much smaller number of deaths/cases than the other two (18, 49) so that they contribute very little to the overall meta-analysis. While some further small studies have been published since (see 8), none are large. For this reason it is worth taking a detailed look at the two larger studies.

The largest of these studies was by Helsing *et al* (49). This involved more heart disease deaths among non-smokers than all the other studies combined. It reported a 24% increase in heart disease risk in women exposed to ETS, based on 988 deaths, and a 31% increase in men, based on 370 deaths. Many features of the study and the results render any conclusion that ETS causes heart disease most insecure:

i) The comparison was of people who lived with a smoker and of those who did not, with no direct adjustment for the number of people in the household. Clearly the larger the household, the more likely it is to contain a

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smoker, so any risk factors related to household size could contribute to the association.

ii) The study was not a properly conducted prospective study, in that data were only collected on whether a given subject had or had not died in Washington County over the 12-year period. Differences in smoking habits and disease status between those who left the county and those who did not may have caused substantial bias.

iii) There was no dose-response relationship in the exposed groups. Indeed, in men the risks (relative to the non-exposed) were somewhat lower with increasing exposure score.

iv) Adjustment for effects of age, marital status, years of school and quality of housing used a procedure that was unclear and which had a huge effect. Thus in women, the passive smoke exposed group had a crude heart disease death rate 34% lower than the non-exposed group. After adjustment it was 24% higher. Such a large effect of adjustment makes one wonder just how contingent the reported results were on the exact list of confounding variables included, the statistical technique used for adjustment, and the accuracy with which the confounding variables were measured.

v) A whole range of factors have been related to heart disease. Among major factors not considered in the study were hypertension and cholesterol level.

While it is difficult to determine the relative importance of the features listed above, it is clear that one must have very considerable reservations about the results from this study.

The Japanese prospective study of Hirayama (18) is superficially very good, being very large, having a long follow-up period and being apparently reasonably representative. However, following detailed scrutiny given to his study following the 1981 paper (52) which really brought ETS to public attention, a number of authors have identified various weaknesses (53, 54, 55). His questionnaire was extremely short and crude by modern standards, severely limiting the number of risk factors studied and the depth to which they could be investigated. The population was only interviewed once with no changes in habits recorded in 16 years. The mortality of his allegedly representative population is too low to reconcile satisfactorily with national rates, indicating that tracing of deaths was incomplete, with deficits varying by age and marital status (53). His statistical presentation is inadequate in a number of ways: the methods used were not appropriate for analysis of long-term cohort studies; rates for heart disease in women were age adjusted to their husband's age rather than their own age; and some basic mistakes in analysis were made. One error, noted in 1981 (54), resulted in enormous inflation of the significance of the lung cancer association. A second, noted more recently (55), concerned the total inconsistency of results for heart disease reported in 1981 and 1984, and was only resolved by Hirayama (56) admitting his earlier data were in error. A number of approaches have been made to Hirayama to release his data for independent verification of his findings by more appropriate statistical methods, but Hirayama has always refused to release his data, which only casts more doubt on his findings. While his findings show a 16% increased risk of heart disease in never smoking women married to smokers which is marginally significant when a dose-related trend test is used, it is difficult to place much faith in his findings.

Although it has been demonstrated above that the risk assessment for heart disease essentially rests on the results from two studies, both of which seem unreliable, a number of other general points can be made. First, there are a very large number of risk factors for heart disease. It is evident that adjustment for these factors in the studies has always been incomplete, and often seriously incomplete. Second, the extent of the association seen in some of these studies, which in some cases is close to that reported in relation to active smoking, is implausibly high when viewed against the extent of the association seen in relation to active smoking. Third, there is a major danger of publication bias. It is notable that the literature is still relatively sparse despite the numerous ongoing studies of heart disease and the fact that heart disease in a non-smoker is probably 50 times or so more common than lung cancer in a non-smoker. Any prospective study that has reported on lung cancer clearly could have done so for heart disease. The fact that the American Cancer Society million person study, which reported for lung cancer (57), has not reported any results on the relationship of heart disease to ETS can reasonably be read as implying no relationship was found in that study. If this is in fact true, and its results were published, the picture from the meta-analysis would change dramatically since the study would involve so many deaths from heart disease in non-smokers.

Cancer other than the lung.

Kawachi *et al* (6) did not include deaths from cancers other than the lung in their risk assessments, but Wells (5) did, although he only made estimates for females since he considered data for males to be too sparse. In fact, there is by now rather more evidence available than Wells considered, and the picture is completely unconvincing as to the effect of ETS exposure.

Of 10 studies providing some evidence, six give no real indication of an effect of ETS. These included two moderate sized case-control studies of bladder cancer (58, 59) which both gave relative risks close to unity, a case-control study of cervix cancer (60) which found no association with spouse smoking after controlling for smoking by the female subject, and a prospective study (47) which found a non-significant relative risk of 1.20 for cancers other than the lung based on 43 deaths. Another study showing no effect was the case-control study of Miller (61) from which an age-adjusted relative risk of 0.97 for lung cancer in relation to husband's smoking history could be calculated. It is interesting to note that Miller, while presenting data by age, did not age-standardise, and gave a relative risk of 1.40, while Wells (5), though he did age-standardise, unaccountably used data for unemployed rather than all women, giving a non-significant, relative risk of 1.25. The largest study showing no effect was the Washington County study on which the Helsing heart disease results (49) were based. A later paper (62) reported that relative risks for all cancer for living with a smoker were 1.01 in males, based on 115 deaths, and 1.00 in females, based on 501 deaths.

Turning now to the four studies that provided at least some suggestion of an effect, the smallest was that by Reynolds *et al* (63). This prospective study found no association between smoking by the spouse and risk of cancer in men, not giving detailed results. In women, a positive association was found, but this was only of marginal significance (p=0.035), and the relative risk of 1.68 had quite wide confidence limits, being based on only 71 cancer deaths, only five of which were considered to be smoking related.

In a large case-control study of cervix cancer in Utah (64), a significant positive trend in risk was noted in relation to various indices of passive smoking exposure. There were many weaknesses in this study, including failure to adjust for religion (42% of cases and 58% of controls were Mormons), large and differential non-response rates, misclassification of smoking status, and failure to adjust adequately for sexual habits. A crude relative risk of 14.8 in relation to ETS exposure for three or more hours per day dropped to 2.96 after adjustment for the reported number of sexual partners of the woman. As number of sexual partners is only an inaccurately measured surrogate of the true sexually related cause of cervix cancer, presumably a sexually transmitted infection, the adjustment will be incomplete and the excess relative risk in relation to ETS may be wholly spurious representing a residual confounding effect of sexual habits (65).

The other two studies reporting a positive association were both cited by Wells (5) and were the major contributors to his risk assessment for cancers other than the lung. The study by Sandler *et al* (66) for which Wells cites a relative risk of 2.0 based on 231 cases of cancer other than the lung, used a mixture of friends or acquaintances of patients and people randomly selected by systematic telephone sampling as controls, a very questionable procedure. Response rates also varied substantially between cases and controls. The unconvincing nature of the findings was heightened by study of the results for individual cancer sites where large effects were claimed for ETS for a number of cancers (breast, thyroid, leukaemia/lymphoma) that have little or no relationship to smoking.

The largest study is that by Hirayama (18, 52, 67). Wells (5) cites a relative risk of 1.11 (95% confidence limits 1.0-1.2) based on 2505 deaths from cancer other than the lung. This is unconvincing for a number of reasons. First, most of the comments made about this study when considering the heart disease results apply. Second, the relative risk is only at best of marginal significance (trend p = 0.05 on a one-tailed test). Third, the association with spouse smoking arises mainly because of elevated risks of brain and breast cancer, cancers that are not smoking related.

The overall evidence for cancer other than the lung is clearly remarkably unconvincing in demonstrating any effect of ETS exposure. Where any association is reported it is generally for cancer sites not affected by active smoking. Wells (5) has great (and unjustified) faith in the epidemiology, claming "these differences in mortality effects are probably real." Because it is certainly true (though as yet unquantified) that smokers have higher ETS exposure than nonsmokers it is *a priori* very difficult to see how an association with any disease could be observed only in response to ETS exposure, a

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view endorsed by IARC (1). Wells argues competing risks might be the explanation, effects of ETS exposure on such cancers as brain, endocrine glands, lymphoma, and breast only occurring in people with a particular susceptibility, and that people with this susceptibility, if they smoke, die first from lung cancer or other smoking-related cancers. This seems a remarkably unattractive and implausible hypothesis, for which there is no supportive evidence. Mortality patterns for lung cancer in terms of age, dose and duration of smoking are well described by models involving no component for variation in susceptibility at all, the response arising from random variation. Of course susceptibility might in fact vary to some extent (68, 69), but hardly so much that any effect in active smokers would be ruled out. The simpler hypothesis that any relationship seen between ETS and cancer of sites other than lung is due to chance or bias seems more plausible.

EXTENDING RISK ASSESSMENT TO COVER ETS EXPOSURE FROM THE WORKPLACE

Wells (5) took account of ETS exposure outside the home in two ways in his risk assessment. First, he estimated the proportion exposed by adding the proportions of never smokers living with ever smokers (taken from the controls of the US based epidemiological studies) to the proportions of all nonsmokers who did not live with a smoker but who where still exposed at home or at work (taken from Friedman (70)). Second, he adjusted relative risk estimates upwards, except in Greece, Japan and Hong Kong, by assuming that nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers. Essentially he assumed that exposure outside the home had the same effect as exposure from the spouse.

Kawachi *et al* (6) estimated the proportion of people exposed at home and at work from surveys. From the relative risk in relation to home exposure, 1.3, they multiplied the excess relative risk, 0.3, by a factor, 4.0, based on Repace and Lowrey's estimate (34) of the relative extent of exposure to the particulate phase of ambient tobacco smoke at work (1.82 mg/day) to at home (0.45 mg/day), thus estimating relative risk of lung cancer in relation to work exposure, 2.2. They commented that "this estimate is consistent with the relative risk of 3.3 (95% confidence interval 1.0-10.5) for never smokers exposed to passive smoking at work reported by Kabat and Wynder (71) in one of the few studies that has distinguished exposure at work from exposure at home. However, we have adopted the more conservative estimate of 2.2".

It is surprising that neither Wells (5) nor Kawachi *et al* (6) seem to have actually taken into account the total epidemiological evidence on lung cancer in relation to workplace exposure. Had they done so (see Table 4) they would have found that overall it gives no indication of a positive association at all, with only four out of eleven relative risk estimates greater than 1.0 and only the single estimate (Kabat 1 - males), selectively cited by Kawachi *et al* (6) even close to being significantly positive. The upper confidence limit for seven of the eleven estimates is less than the estimate of 2.2 used in their risk assessment.

Most lung cancer cases occur at an age after people have retired. While Wells (5) adjusts the exposed fraction down with increasing age, Kawachi *et al* (6) make no such adjustment, assuming that their unjustifiably high relative risk of 2.2 in relation to workplace exposure operates at age 80 as at age 40.

The estimates by Kawachi *et al* (6) of risk due to workplace exposure from risk due to at home exposure are in any case methodologically unsound. Even assuming (and these are very big assumptions), that meta-analysis gives unbiassed estimates, that risk is linearly related to extent of exposure to smoke constituents, and that the estimates of relative exposure at work and at home are valid, the equation they used is totally incorrect. The formula only makes sense for a comparison of those exposed at work and not elsewhere with those exposed at home and not elsewhere. If at home and at work exposure are positively correlated (as is likely) double counting of deaths arises. In the extreme situation where everyone is exposed to both or to neither source, their method for estimating deaths due to at home exposure yields an answer appropriate for both exposures combined. Using their procedure, which would then multiply up deaths due to ETS by five, might lead to there being more deaths due to ETS than actually occur in all!

The validity of the factor of 4 for relative exposure at work to at home is anyway very dubious. A recent large survey in London (74) found little difference between particulate matter levels measured in the home and at work. Indeed where smoking took place, the level at work was <u>less</u> than at home.

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TABLE 4 Reported relative risks of lung cancer in relation to ETS exposure at work.

Study	(ref)	Sex	Index of exposure	Relative risk (95% conf.limits)
Garfinkel	(42)	Female	Smoke exposure at work in last 5 years	0.88(0.66-1.18)
		Female	Smoke exposure at work in last 25 years	0.93(0.73-1.18)
Kabat 1	(71)	Female	Current exposure on regular basis to tobacco smoke at work	0.68(0.32-1.47)
		Male	Current exposure on regular basis to tobacco smoke at work	3.27(1.01-10.6)
Kabat 2	(72)	Female	Exposed to ETS at work (ever)	1.00(0.49-2.06)
		Male	Exposed to ETS at work (ever)	0.98(0.46-2.10)
Lee	(24)	Female	Passive smoke exposure at work	0.63(0.17-2.33)
		Male	Passive smoke exposure at work	1.61(0.39-6.60)
Shimizu	(73)	Female	Someone at working place smokes	1.20(0.44-1.37)
Varela	(41)	Both	150 person/years smoking in the workplace	0.91(0.80-1.04)
Wu	(20)	Female	Passive smoke exposure at work	1.3 (0.5-3.3)

OTHER ISSUES

Extension of risk assessments to workplace ETS and heart disease deaths.

While the use of epidemiological data to estimate the number of deaths from lung cancer among never smokers is dubious, extension of these estimates to other diseases and to workplace exposure is even more so. This highlights the invalidity of the estimates by Kawachi *et al* (6) where of a total of 273 deaths per year due to ETS among never smokers, only 4 are from lung cancer due to at home ETS exposure, while as many as 152 are from ischaemic heart disease due to at work ETS exposure. The fragility of the confidence limits, 112 to 442, for the overall total of 273 is obvious. In no sense can we be confident that the true answer lies in this range. The estimate is cast in an even poorer light when one realises that the factor of 4 used to calculate lung cancer relative risks at work from those at home is also used for heart disease. What is the justification for that? The basis for the factor is relative particulate matter exposure, widely thought irrelevant to heart disease aetiology. It is notable that their resultant heart disease relative risk estimates for at work exposure are, implausibly, larger than those generally reported in relation to active smoking.

Extension of risk assessments to ex-smokers.

Wells (5) and Repace and Lowrey (7) estimate numbers of deaths due to ETS among never smokers and ex-smokers combined. They assume risk estimates based on results for never smokers are applicable also to ex-smokers. Neither paper discusses the problems implicit in this approach. In the first place there is no direct epidemiological evidence on risk in relation to ETS exposure for ex-smokers with the limited exception of the study by Varela (41) which found no evidence of an effect of ETS in either never smokers or long term ex-smokers. Nor is there any evidence on levels of ETS exposure in ex-smokers as distinct from never smokers. Without direct evidence the assumption that risk increases in relation to level of ETS exposure in ex-smokers to the same extent that it does in never smokers seems remarkably simplistic. Might not effects of ex-smoking interact with those of ETS (if any)? Might not the situation depend on how long ago the smoker has given up, or why? There seems no scientific justification whatsoever for extrapolating estimates to ex-smokers.

Extrapolation from one country to another.

Kawachi *et al* (6) do not discuss the validity of calculating estimates for New Zealand when all their relevant source data comes from other countries. Their answer depends heavily on the US based factor of 4 used for relative exposure at work to at home. As noted above a UK study (68) found a factor less than 1. Which is relevant for New Zealand?

Variations in relative risk of lung cancer by age.

As discussed by Wells (5) and in the NRC report by Robins (4), if the relationship between

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ETS and lung cancer risk depended on age, it would be appropriate to take this into account in the risk assessment. In fact only the study of Hirayama (18, 67) presents data by age, other investigators implicitly assuming that the relative risk is invariant of age. Using a relative risk estimate of 1.44 as applying to all age groups, Wells calculated there would be 992 deaths per year due to ETS exposure. Wells noted that Hirayama's data actually indicated "a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75" and used these data to "develop a second death calculation assuming a declining relative risk but still normalized to 1.44" arriving at a slightly lower estimate of 911 deaths per year. Wells' calculations mislead in a number of ways. First, he used as source material data on risk by age of the husband (67) when more appropriate data by age of the wife were available (18). Second, he used data for ages 60-69 and 70-79 combined as applicable at "approximately age 75", concealing the fact that the relative risk estimate at age 70-79 is actually 0.70. If one uses data in Wells' Table 6 for never smoker death rates, nonsmoker populations and fractions exposed by age, and one uses Hirayama's actual relative risks by age of the wife (18), then it can be shown (Table 5) that allowing for variation in risk by age very substantially affects estimates. Thus, for the 40-79 age group, one arrives at an estimate of 858 deaths due to ETS if one assumes age invariance, but one actually arrives at an estimate of 964 deaths saved by ETS if one uses Hirayama's data directly. The relative risk estimate for the 70-79 year age group is certainly unreliable, being based on only 6 deaths in the Hirayama study (as against 46, 91 and 57 for ages 40-49, 50-59, 60-69), so in Table 5 estimates of deaths are also shown using a combined relative risk for the age groups 60-69 and 70-79. This gives an estimate of 299 deaths due to ETS, substantially less that that assuming risk is invariant of age. While there are many problems in applying the Hirayama estimates, including the fact that Wells' Table 6 is based on age at death whereas Hirayama's data are based on age at start of the study, Wells' paper conceals the major problems which have been given detailed attention by a number of authors (75, 76). Reliable data broken down by age are clearly needed.

How many lung cancer deaths are there in total among never smokers?

In 1985 in the USA, there were a total of 83,854 deaths from lung cancer among males and 38,702 among females (77). In his Tables 6 and A1, Wells (5) gives estimates of death rates among never smokers which, if applied to the age-specific population estimates of never smokers, yield 1,907 deaths among males and 4,232 deaths among females, respectively 2.3% and 10.9% of the total deaths from lung cancer.

TABLE 5 Numbers of lung cancer deaths per year among US nonsmokers occurring in the population aged 40-79 based on Hirayama's (18) estimates of relative risk by age of wife

	Risk assumed invariant of age		Risk assumed to vary with age	
Age	Relative risk	Deaths	Relative risk*	Deaths*
40-44	1.45	32	2.76	69
45-49	1.45	40	2.76	85
50-54	1.45	58	1.72	79
55-59	1.45	89	1.72	122
60-64	1.45	119	1.12(0.97)	39(-11)
65-69	1.45	165	1.12(0.97)	54(-15)
70-74	1.45	170	0.19(0.97)	-740(-15)
75-79	1.45	185	0.19(0.97)	-672(-15)
Total		858		-964(299)

* Bracketed items assume common estimates for 60-69 and 70-79 age group.

Elsewhere (78), I have reviewed the proportion of lung cancers occurring among never smokers in a range of recent epidemiological studies of Western populations. This gave an average of 2.4% for males and 13.2% for females, equivalent to 2,012 and 5,109 deaths respectively, reasonably close to the estimates of Wells.

Other authors have suggested there are more deaths than this. Thus in the 1986 NRC report (4) Robins quoted estimates of roughly 5,200 deaths for males and 7,000 for females among U.S.

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never smokers in 1985, while Repace and Lowrey (7) cite Kuller *et al* (36) for an estimate of 6000 to 8000 lung cancer cases each year in US never smoking women.

Three points arise. First, there is considerable uncertainty about the number of lung cancer deaths among never smokers.

Second, if the lower estimates, which total about 6,000-7,000 deaths in the two sexes combined, are used, then many of the epidemiologically based estimates shown in Table 2 are totally unreasonable. Even if (implausibly) everyone were assumed to be exposed to ETS with risk doubled as a result the estimated number of lung cancer deaths occurring among never smokers would only be 3,000-3,500, and yet the four highest estimates in Table 2 all exceed this.

Third, none of the estimates of total lung cancer deaths among never smokers cited above make any adjustment for misclassification of smoking status, all taking self-reported smoking habits at face value. Starting with the first estimate cited above of 6,139 deaths for the sexes combined, one can readily calculate that, if 1% of ever smokers were assumed to deny smoking on interview, this figure would fall by over a thousand to 4,972. This underlines the unreasonableness of the higher estimates in Table 2.

DISCUSSION

In the USA in 1985 there were some 120,000 deaths from lung cancer. Although estimates of the total number occurring among never smokers of up to around 12,000 have been cited, more reasonable estimates seems to be about 5,000 to 6,000. In attempting to estimate how many of these occur as a result of ETS exposure, one has to decide whether to base one's estimate on the epidemiological evidence on ETS and lung cancer or on the dosimetric evidence on exposure to relevant smoke constituents of ETS exposed nonsmokers and smokers. It is abundantly clear that the two methods of estimation give very different answers. Thus, while estimates based on retained particulate matter give tens of deaths and those based on nicotine or respirable suspended particulates give hundreds, the epidemiologically based estimates all give thousands of deaths. Which answer, if any, one accepts depends to a large extent on the faith one places on the different types of evidence. Wells (5), Kawachi *et al* (6) and Repace and Lowrey (7) accept the epidemiology essentially at face value and pay little or no attention to its poor quality and very obvious weaknesses. They either ignore the dosimetric evidence (6), do not make it clear that it gives different answers and/or dismiss it as inconsistent with the epidemiology (7), or invoke mechanisms to explain the discrepancy which are scientifically unappealing (5). It seems to this author that the epidemiological evidence is untrustworthy and that, between the two, the dosimetric evidence is preferable. Of course problems remain both in choosing the appropriate index of exposure to use and in selecting the appropriate dose response curve at low doses (with the possibility of a threshold), but it seems clear that this approach is better than one which leads to such implausibly high figures.

When one restricts attention to lung cancer, to never smokers and to ETS exposure from the spouse, one is at least operating in an area where the epidemiological evidence indicates an association. When one extends risk assessment to other diseases, to ex-smokers and to ETS exposure in the workplace one is stretching the limits of what is science. There essentially is no evidence on possible effects of ETS in ex-smokers and little reason to expect that any effects, if they exist, will be the same as in never smokers. There is some evidence on ETS exposure in the workplace, but this shows no association at all with lung cancer risk. The epidemiological evidence on ETS in relation to deaths from causes other than lung cancer is unconvincing, and no scientific authority has claimed cause and effect.

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Review

Involuntary Smoking in the Restaurant Workplace

A Review of Employee Exposure and Health Effects

Michael Siegel, MD, MPH

Objective.—To determine the relative exposure to environmental tobacco smoke for bar and restaurant employees compared with office employees and with nonsmokers exposed in the home (part 1) and to determine whether this exposure is contributing to an elevated lung cancer risk in these employees (part 2).

Data Sources.—MEDLINE and bibliographies from identified publications.

Study Selection.—In part 1, published studies of indoor air quality were included if they reported a mean concentration of carbon monoxide, nicotine, or particulate matter from measurements taken in one or more bars, restaurants, offices, or residences with at least one smoker. In part 2, published epidemiologic studies that reported a risk estimate for lung cancer incidence or mortality in food-service workers were included if they controlled, directly or indirectly, for active smoking.

Data Extraction.—In part 1, a weighted average of the mean concentration of carbon monoxide, nicotine, and respirable suspended particulates reported in studies was calculated for bars, restaurants, offices, and residences. In part 2, the relative lung cancer risk for food-service workers compared with that for the general population was examined in the six identified studies.

Data Synthesis.—Levels of environmental tobacco smoke in restaurants were approximately 1.6 to 2.0 times higher than in office workplaces of other businesses and 1.5 times higher than in residences with at least one smoker. Levels in bars were 3.9 to 6.1 times higher than in offices and 4.4 to 4.5 times higher than in residences. The epidemiologic evidence suggested that there may be a 50% increase in lung cancer risk among food-service workers that is in part attributable to tobacco smoke exposure in the workplace.

Conclusions.—Environmental tobacco smoke is a significant occupational health hazard for food-service workers. To protect these workers, smoking in bars and restaurants should be prohibited.

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THE ADVERSE health effects of environmental tobacco smoke (ETS) exposure are now well recognized.[1-4] The Environmental Protection Agency classified ETS as a group A carcinogen and estimated that it causes about 3000 lung cancer deaths per year in nonsmokers.[3] The workplace is a major source of ETS exposure, and the National Institute for Occupational Safety and Health has recommended that involuntary exposure to tobacco smoke be eliminated by prohibiting smoking in the workplace.[5] Many state and local governments have responded to this recommendation by prohibiting smoking in public and/or private workplaces.[6]

Many local governments have regulated smoking in restaurants.[7] These efforts have generally focused on protecting the public from ETS (Hatfield L. Face-off: smoking in restaurants? *San Francisco Examiner*. February 27, 1992: A1). However, restaurants are also workplaces, and because restaurant employees spend a much longer time in the restaurant than do patrons, ETS exposure is more likely to result in adverse health effects for them.

This review assesses the potential health hazard of ETS exposure for bar and restaurant employees. There are two questions considered. First, what is the relative exposure to ETS for bar and restaurant employees compared with employees of other businesses and with individuals who live in a home with a smoker? Second, does ETS exposure in bars and restaurants produce an elevated lung cancer risk among these workers? To answer the first question, published indoor air quality data for bars, restaurants, offices, and residences were reviewed. To answer the second question, the epidemiologic studies of lung cancer risk in food-service workers were reviewed.

METHODS

Literature Review

A literature search was carried out using the National Library of Medicine MEDLINE database to locate published studies that reported measurements of tobacco constituents in indoor air and studies of occupational lung cancer risk in food-service workers. Bibliographies from each publication were reviewed to identify additional relevant citations.

In part 1, studies were included if they met the following criteria: (1) reported the mean concentration of carbon monoxide, nicotine, or respirable suspended particulates from measurements taken in one or more restaurants, bars, offices, or residences with at least one smoker; (2) did not include measurements taken in designated smoking areas; and (3) did not include measurements taken under smoke-free conditions. Thus, these studies include measurements in restaurants and offices that allowed smoking anywhere, or in the nonsmoking areas of restaurants and offices that restricted smoking to a designated area. Measurements in residences were taken in the presence of at least one smoker. In addition to individual studies obtained through the computer search, three published reviews were

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Table 1.—Indoor Air Concentrations of Carbon Monoxide, Nicotine, and Respirable Suspended Particulates in Restaurants, Bars, Offices, and Residences*

Constituent	No. of Studies	No. of Sites Sampled	Weighted Mean†	Range	Ratio‡
Carbon monoxide, ppm					
Offices	12	1161	3.0	1.0-3.3	1.0
Restaurants	12	229	5.1	0.5-9.9	1.7
Bars	10	32	11.6	3.1-17	3.9
Nicotine, μg/m³					
Offices	22	940	4.1	0.8-22.1	1.0
Residences	7	91	4.3	1.6-21	1.0
Restaurants	17	402	6.5	3.4-34	1.6
Bars	10	25	19.7	7.4-65.5	4.8
Particulates, μg/m³					
Offices	19	912	57	6-256	1.0
Residences	13	624	78	32-700	1.4
Restaurants	12	211	117	27-690	2.0
Bars	10	16	348	75-1320	6.1

*Data from Sterling et al,[8] Repace,[9] Guerin et al,[10] and Turner et al.[11] No studies met the inclusion criteria for measurement of carbon monoxide in residences.

†Weighted average of individual study mean concentrations for all measurements taken. Weights used were the number of restaurants, bars, offices, or homes sampled.

‡Ratio of weighted mean restaurant, bar, or residence to weighted mean office concentration.

helpful in ensuring that most of the relevant literature was included in the analysis. First, Sterling et al[8] reviewed the published literature on air sampling of tobacco constituents as of 1982. Second, Repace[9] reviewed the results of about 50 studies of indoor ETS concentrations that were published before 1987. Third, the most recent and extensive review of the literature, published by Guerin et al[10] in 1992, reports the results of nearly 100 air-sampling studies. Finally, data from the largest single study of indoor ETS levels, in which Turner et al[11] tested 585 office environments, were included in this review and analysis. It should be noted that data from individuals or groups allied with and funded by the tobacco industry[11] were included in the analysis.

In part 2, studies were included if they met the following criteria: (1) reported a risk estimate of lung cancer incidence or mortality in food-service workers compared with other workers or with the general population; and (2) controlled, directly or indirectly, for the confounding effects of active smoking.

Data Analysis

In part 1, a weighted average of the mean carbon monoxide, nicotine, and respirable suspended particulates concentrations reported in each of the studies was calculated for bars, restaurants, offices, and residences. The weight given to each study was the number of separate restaurants, offices, or homes sampled. This weighting procedure resulted in heavier weighting of studies that reported the means of a large number of separate office or restaurant measurements. These studies are more likely to reflect typical workplace concentrations than those measuring concentrations in a single workplace.

In part 2, no attempt was made to statistically pool the individual lung cancer risk estimates, owing to the small number of studies and the variability in study designs.

RESULTS

Part 1: ETS Levels in Restaurant Air

The mean restaurant ETS constituent concentrations are between 1.6 and 2.0 times higher than those in the office workplaces studied, and 1.5 times higher than levels in homes with at least one smoker present (Table 1). Mean concentrations of ETS constituents in bars are 3.9 to 6.1 times higher than in the office workplaces, and 4.4 to 4.5 times higher than in the residences.

One must be cautious in comparing ETS exposure in the home and workplace based only on ETS concentrations in ambient air because the duration of exposure is different in each environment. Repace[9] has shown that total exposure is proportional to both concentration and duration of exposure. Based on time-budget studies that have estimated the average amount of time spent by working persons in various environments, the average US adult spends about 14 hours in the home and 6 hours in the workplace per day.[12] Allowing for 8 hours of sleep per day, and assuming that persons exposed to ETS at home are exposed during all waking hours, the duration of exposure is similar in the two environments (6 hours). Thus, total exposure to ETS is likely to be at least 1.5 times higher for restaurant workers than for persons who live with a smoker, and at least 4.4 times higher for bar workers than for individuals with only domestic ETS exposure.

Part 2: Health Effects of Restaurant ETS Exposure

Eleven studies have examined lung cancer risk in food-service workers without controlling for active smoking.[13-23] These studies were excluded from the analysis. Six studies have examined lung cancer risk in food-service workers, controlling for active smoking and other potential confounding variables.[24-32] One of these was a historical cohort study that examined occupational lung cancer mortality. Five were case-control studies that included incident lung cancer cases (Table 2).

Investigators in the California Occupational Mortality studies[24-27] reviewed California's mortality data from 1979 through 1981 by occupation.[24-27] Crude standardized mortality ratios (SMRs) were calculated for food-service workers. Singleton and Beaumont[26] and Beaumont et al[27] then attempted to control for smoking, alcohol, and socioeconomic status indirectly by adjusting for national occupational smoking and alcohol use rates (imputed from National Health Interview Survey data and average occupational socioeconomic status). For white male food-service workers, the unadjusted lung cancer SMR was 105% and the adjusted SMR was 125% (95% confidence interval [CI], 90% to 169%). For male bartenders, the adjusted SMR was 152% (95% CI, 118% to 192%). For white waitresses, the crude SMR was 368% and the adjusted SMR was 148% (95% CI, 125% to 174%).

Williams et al[28] conducted a case-control study using cancer mortality data from the Third National Cancer Survey. Occupational history and a range of potential confounders were determined by interview. Odds ratios (ORs) for working in various occupations were determined for a variety of cancer types, adjusted for smoking, alcohol, income, and education. For female food-service workers, the adjusted lung cancer OR was 1.88. For male food-service workers, no risk estimate was reported owing to the small number of cases (two).

Lerchen et al[29] studied the relationship between occupation and lung cancer among males in a case-control study using the New Mexico Tumor Registry. Cases and population-based controls were interviewed to obtain occupational and smoking histories. For males employed in the "eating and drinking establishment industry" category, an adjusted OR of 1.6 (95% CI, 0.8 to 2.9) was reported.

Schoenberg et al[30] examined the relationship between occupation and lung cancer in New Jersey males in a case-control study. Cases obtained from a state health department reporting system and

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Table 2.—Studies of Lung Cancer Risk in Food-Service Workers, Controlled for Active Smoking*

Source	Subjects	Study Design	Risk Estimate (95% Confidence Interval)	No. of Cases or Deaths	Additional Confounders Controlled
		Males			
Singleton and Beaumont[28]	California (deaths)	Historical cohort			Age, sex, race, SES, alcohol
	Bartenders		SMR=1.52 (1.18-1.92)	69	
	Other food-service workers		SMR=1.25 (0.90-1.69)	42	
Lerchen et al[29]	New Mexico (incident cases) Eating and drinking industry workers	Case-control	OR=1.6 (0.8-2.9)	26	Age, sex, race, diet
Schoenberg et al[30]	New Jersey (incident cases)	Case-control			Age, sex race, SES, diet
	Bartenders		OR= . . . (1.2-1.3)†	29	
	Other food-service workers		OR= . . . (1.1-1.2)†	37	
Zahm et al[31]	Missouri food-service workers (incident cases)	Case-control	OR=1.8 (1.0-3.5)	24	Age, sex, race
		Females			
Singleton and Beaumont[28]	California waitresses (deaths)	Historical cohort	SMR=1.48 (1.25-1.74)	149	Age, sex, race, SES, alcohol
Williams et al[26]	US food-service workers (incident cases)	Case-control	OR=1.88	12	Age, sex, race, SES, alcohol
Keller and Howe[32]	Illinois females employed in eating and drinking places; nonsmokers (incident cases)	Case-control	OR=1.92 (1.21-3.07)	Not given	Age, sex, race

*SMR indicates standardized mortality ratio; SES, socioeconomic status; and OR, odds ratio.
†Specific OR not given in source cited.

population-based controls were interviewed to obtain occupational, smoking, and dietary histories. The adjusted OR for male bartenders was between 1.2 and 1.3, and for other food-service workers was between 1.1 and 1.2.

Zahm et al[31] conducted a case-control study to determine (after adjusting for smoking) the relationship between lung cancer and occupation. Data from the Missouri Cancer Registry, which includes occupational and smoking histories, were reviewed for white male lung cancer cases diagnosed between 1980 and 1985. The adjusted OR for food-service workers was 1.8 (95% CI, 1.0 to 3.5).

Keller and Howe[32] performed a case-control study using all incident lung cancers among nonsmokers entered in the Illinois Cancer Registry from 1985 to 1987. The controls were nonsmoking colon cancer cases. Unlike the other five studies, Keller and Howe's study controlled for active smoking by specification rather than adjustment. Only nonsmokers were included in the analysis. The OR for lung cancer in females employed in eating and drinking places was 1.92 (95% CI, 1.21 to 3.07). No risk estimate was given for males.

Taken together, these studies suggest that there is an excess lung cancer risk of approximately 50% (range 10% to 90%) among food-service workers compared with the general population, controlling for active smoking. In the two studies that examined bartenders and other food-service workers separately, this excess lung cancer risk was found for both groups of workers.[28,30] Thus, it appears that there is an elevated lung cancer risk in both bar and restaurant workers that persists after controlling for active smoking.

COMMENT

The availability of ambient air survey data on ETS levels in more than 1000 offices, more than 400 restaurants, and more than 600 homes provides an opportunity to estimate the relative ETS exposure of bar and restaurant workers compared with that of office workers and with that of individuals who live with a smoker. In this analysis, ETS exposure for restaurant workers was estimated to be 1.6 to 2.0 times higher than for office workers, and at least 1.5 times higher than for persons who live with a smoker. For bar workers, ETS exposure was estimated to be 3.9 to 6.1 times higher than for office workers, and at least 4.4 to 4.5 times higher than for persons exposed in the home. An attempt was made to determine whether this increased estimated workplace ETS exposure in bars and restaurants produces an increase in lung cancer risk for these workers. In six epidemiologic studies that controlled for active smoking, an excess lung cancer risk of approximately 50% (range, 10% to 90%) was found for food-service workers compared with the general population. This excess risk could well be due to the increased ETS exposure of food-service workers. However, there are several alternative explanations that must be considered.

First, residual confounding by smoking might explain the elevation in lung cancer risk for food-service workers. There are several reasons to believe that this is not the case. Three case-control studies that controlled for smoking[29-31] involved detailed smoking histories. Smoking status was measured as a categorical[31] or continuous variable,[29,30] incorporating duration and intensity of smoking. Moreover, the adjustment for smoking produced little change in the OR for males. Lerchen et al[29] reported a change in OR from 1.7 to 1.6 when smoking was added to the regression model. Schoenberg et al[30] reported a change in OR of no more than 0.1 for food-service workers when smoking was considered. The finding of an elevated lung cancer risk among female food-service workers in a study restricted to nonsmokers[32] adds further evidence that residual confounding by smoking is unlikely to explain the elevated lung cancer risk among food-service workers.

Second, confounding by a variable known to be associated with both lung cancer and food-service employment might explain the observed association. The most important considerations are age, sex, race, socioeconomic status, and diet (saturated fat and β-carotene [vitamin A] intake[33]). However, age, sex, and race were controlled in all six studies (Table 2). Socioeconomic status was controlled in three studies, and diet in two. Vitamin A intake, but not saturated fat intake, was specifically measured in these studies.[29,30]

Third, publication bias might explain why the six published studies reported an increased lung cancer risk in food-service workers. However, since these studies examine the relationship between lung cancer and a wide variety of occupations, they will almost certainly find a positive association with one or more occupations. Therefore, it is not plausible that studies finding no association between lung cancer and food-service employment have been differentially rejected or not submitted for publication.

Finally, the observed increase in lung cancer risk among food-service workers might be due to a carcinogenic exposure other than ETS. The most important consideration is exposure to cooking fumes. Air samples of cooking fumes have been shown to be mutagenic in the Ames assay,[34] and cooks have been shown to have elevated risks of respiratory tract cancers.[16,17,20,25-28] However, there are several reasons to believe that exposure to cooking fumes is not contributing substantially to the increased lung cancer risk among food-service workers. First, a study of the mutagenicity of restaurant air[34] suggests that ETS is the major contributor to the mutagenicity of air from dining areas. In this study, the mutage-

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nicity of air from dining areas was closely correlated with smoker density, but had no relation to the mutagenicity of air from kitchen samples. Second, ventilation in restaurants is generally designed to prevent cooking fumes from escaping into dining areas.[34] Average ventilation rates over cooking surfaces in four restaurants studied met the minimum requirements of the American Conference of Governmental Industrial Hygienists.[39] The most important source of exposure to cooking fumes in these restaurants was contamination in "cook's breathing zones during active work processes."[34] Third, a time-budget study of cooks found that only 33% to 60% of a cook's shift is spent over cooking surfaces.[34] Food-service personnel would be expected to spend a much lower percentage of their time in contact with air contaminants over cooking surfaces. Finally, the studies that have controlled for active smoking and examined lung cancer risk in cooks have not reported an elevated risk for these workers. Singleton and Beaumont[26] found an adjusted lung cancer SMR of 91% for males and 102% for females. Schoenberg et al[30] reported an adjusted OR of 0.9 for cooks. It is quite possible that the increased lung cancer risk among cooks is due to confounding by active smoking. Smoking rates in male cooks are 30% higher than in the general male population.[40]

An elevation in lung cancer risk attributable to ETS exposure in the restaurant workplace is plausible. Since domestic ETS exposure is associated with a relative risk for lung cancer of 1.3[1-3,35] and this review estimated that typical restaurant ETS exposure is at least 1.5 times higher than domestic exposure, an excess lung cancer risk over 30% in restaurant workers, compared with unexposed nonsmokers in domestic settings, would be expected. High levels of restaurant air mutagenicity[34] and increased levels of urine mutagenicity[41] and 3-aminobiphenyl,[42] a suspected carcinogenic hemoglobin adduct, have been demonstrated in ETS-exposed restaurant workers.

The effects of domestic ETS exposure[1-3] and ETS exposure in the workplace in general[5] have been recognized. This review of exposure to and health effects of ETS in bar and restaurant workplaces specifically addresses ETS as an important occupational health hazard for food-service workers. Public health efforts to regulate smoking in bars and restaurants can no longer focus only on protecting the patron. Food-service workers must be afforded the same public health protection as other workers. To protect these workers from the hazards of ETS, smoking should be prohibited in bars and restaurants.

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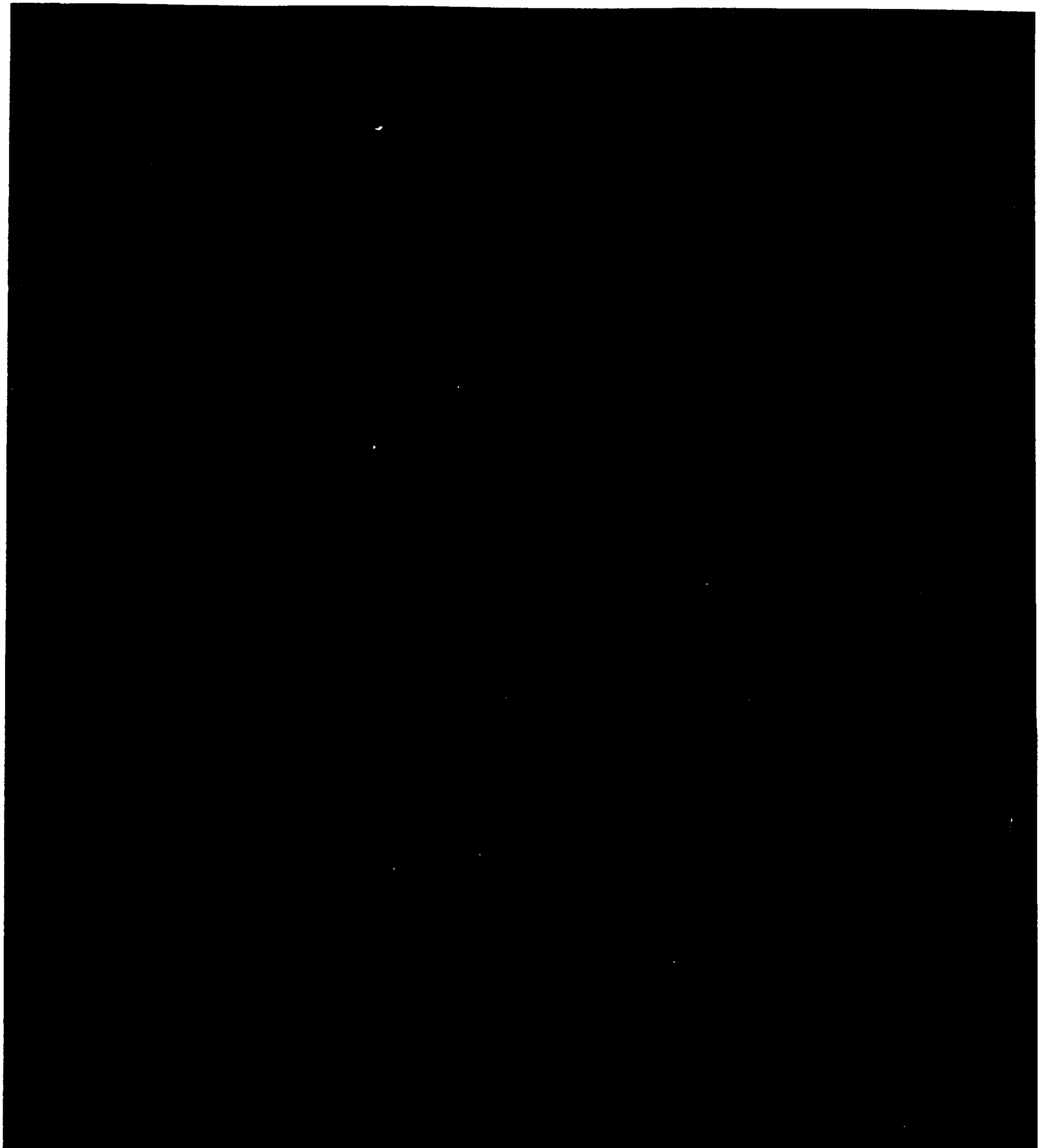

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